PATENT
Docket No. 56286US003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicant(s): PARTHASARATHY et al. | Group Art Unit: 1651 |
| Serial No.: 09/841,264<br>Confirmation No.: 5359 | Examiner: David M. Naff |
| Filed: April 24, 2001 | |
| For: BIOLOGICAL SAMPLE PROCESSING METHODS AND COMPOSITIONS THAT INCLUDE SURFACTANTS | |

## DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Loren D. Albin, declare and say as follows:

1. I, Loren D. Albin, am an attorney registered to practice before the U.S. Patent and Trademark Office under Registration No. 37,763.

2. I have read and am familiar with present U.S. Pat. Application Serial No. 09/841,264. On page 13, lines 29-30, the specification recites "U.S. Patent Application Serial No. 09/710,184 filed on November 10, 2000," which is incorporated by reference at page 28, lines 7-8 of the present specification, which states that "[p]atents, patent applications, and publications disclosed herein are hereby incorporated by reference (in their entirety) as if individually incorporated."

3. I have read and am familiar with U.S. Pat. Application Serial No. 09/710,184, attached herewith as EXHIBIT A, which was incorporated by reference in present application Serial No. 09/841,264, as described herein above in paragraph 2. On page 5, lines 22-23, the specification of application Serial No. 09/710,184 recites "U.S. Provisional Patent Application

Serial No. 60/214,642 filed on June 28, 2000," which is incorporated by reference at page 22, lines 19-20 of application Serial No. 09/710,184, which states that "[p]atents, patent applications, and publications disclosed herein are hereby incorporated by reference as if individually incorpoarated."

4. I have read and am familiar with U.S. Provisional Pat. Application Serial No. 60/214,642, attached herewith as EXHIBIT B, which was incorporated by reference in present application Serial No. 09/841,264, as described herein above in paragraphs 2 and 3. The Examiner's attention is drawn to Figures 1, 18, and 19 of application Serial No. 60/214,642.

5. I have read and am familiar with the Preliminary Amendment submitted February 28, 2002, in present application Serial No. 09/841,264. The preliminary amendment added Figures 2, 3, and 4.

6. On information and belief, Figures 2, 3, and 4 added in the Preliminary Amendment submitted February 28, 2002, in present application Serial No. 09/841,264, consists of the same material incorporated by reference in Figures 1, 18, and 19 of application Serial No. 60/214,642, as described herein above in paragraphs 2, 3, and 4, except that values of reference numerals have been changed for clarification.

7. I further declare that statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

February 19, 2004
Date

Attorney: Loren D. Albin
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CERTIFICATE UNDER 37 CFR §1.10::
"Express Mail" mailing label number: EV 405 459 151 US Date of Deposit: February 19, 2004
I hereby certify that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: ______ Name: Rachel Gagliardi-Graham

# Exhibit B



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Bib Data Sheet

| SERIAL NUMBER 60/214,642 | FILING DATE 06/28/2000 RULE – | CLASS – | GROUP ART UNIT – | ATTORNEY DOCKET NO. 55266USA99 |
|---|---|---|---|---|

**APPLICANTS**
William Bedingham, Woodbury, MN ;

** CONTINUING DATA *************************

** FOREIGN APPLICATIONS ********************

IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 09/13/2000

| Foreign Priority claimed ☐ yes ☐ no<br>35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance<br>Verified and Acknowledged ____ Examiner's Signature Initials | STATE OR COUNTRY | SHEETS DRAWING | TOTAL CLAIMS | INDEPENDENT CLAIMS |
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| | MN | 11 | – | – |

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**TITLE**

Thermal processing devices and methods

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PATENT
Docket No. 55266USA99

# SAMPLE PROCESSING DEVICES, SYSTEMS AND METHODS

## Technical Field

The present invention relates to devices, methods and systems for thermal processing of sample materials, such as methods used to amplify genetic materials, etc.

## Background

Many different chemical, biochemical, and other reactions are sensitive to temperature variations. Examples of thermal processes in the area of genetic amplification include, but are not limited to, Polymerase Chain Reaction (PCR), Sanger sequencing, etc. The reactions may be enhanced or inhibited based on the temperatures of the materials involved. Although it may be possible to process samples individually and obtain accurate sample-to-sample results, individual processing can be time-consuming and expensive.

One approach to reducing the time and cost of thermally processing multiple samples is to use a device including multiple chambers in which different portions of one sample or different samples can be processed simultaneously. When multiple reactions are performed in different chambers, however, one significant problem can be accurate control of chamber-to-chamber temperature uniformity. Temperature variations between chambers may result in misleading or inaccurate results. In some reactions, for example, it may be critical to control chamber-to-chamber temperatures within the range of $\pm 1$°C or less to obtain accurate results.

The need for accurate temperature control may manifest itself as the need to maintain a desired temperature in each of the chambers, or it may involve a change in temperature, e.g., raising or lowering the temperature in each of the chambers to a desired setpoint. In reactions involving a change in temperature, the speed or rate at which the temperature changes in each of the chambers may also pose a problem. For example, slow temperature transitions may be problematic if unwanted side reactions occur at intermediate temperatures. Alternatively, temperature transitions that are too rapid may

cause other problems. As a result, another problem that may be encountered is comparable chamber-to-chamber temperature transition rate.

In addition to chamber-to-chamber temperature uniformity and comparable chamber-to-chamber temperature transition rate, another problem may be encountered in those reactions in which thermal cycling is required is overall speed of the entire process. For example, multiple transitions between upper and lower temperatures may be required. Alternatively, a variety of transitions (upward and/or downward) between three or more desired temperatures may be required. In some reactions, e.g., polymerase chain reaction (PCR), thermal cycling must be repeated up to thirty or more times. Thermal cycling devices and methods that attempt to address the problems of chamber-to-chamber temperature uniformity and comparable chamber-to-chamber temperature transition rates, however, typically suffer from a lack of overall speed -- resulting in extended processing times that ultimately raise the cost of the procedures.

One or more of the above problems may be implicated in a variety of chemical, biochemical and other processes. Examples of some reactions that may require accurate chamber-to-chamber temperature control, comparable temperature transition rates, and/or rapid transitions between temperatures include, e.g., the manipulation of nucleic acid samples to assist in the deciphering of the genetic code. *See, e.g.,* T. Maniatis et al. *Molecular Cloning, A Laboratory Manual,* Cold Spring Harbor Laboratory (1982). Nucleic acid manipulation techniques include amplification methods such as polymerase chain reaction (PCR); target polynucleotide amplification methods such as self-sustained sequence replication (3SR) and strand-displacement amplification (SDA); methods based on amplification of a signal attached to the target polynucleotide, such as "branched chain" DNA amplification; methods based on amplification of probe DNA, such as ligase chain reaction (LCR) and QB replicase amplification (QBR); transcription-based methods, such as ligation activated transcription (LAT) and nucleic acid sequence-based amplification (NASBA); and various other amplification methods, such as repair chain reaction (RCR) and cycling probe reaction (CPR). Other examples of nucleic acid manipulation techniques include, e.g., Sanger sequencing, ligand-binding assays, etc.

One common example of a reaction in which all of the problems discussed above may be implicated is PCR amplification. Traditional thermal cycling equipment for

conducting PCR uses polymeric microcuvettes that are individually inserted into bores in a metal block. The sample temperatures are then cycled between low and high temperatures, e.g., 55°C and 95°C for PCR processes. When using the traditional equipment according to the traditional methods, the high thermal mass of the thermal cycling equipment (which typically includes the metal block and a heated cover block) and the relatively low thermal conductivity of the polymeric materials used for the microcuvettes result in processes that can require two, three, or more hours to complete for a typical PCR amplification.

One attempt at addressing the relatively long thermal cycling times in PCR amplification involves the use of a device integrating 96 microwells and distribution channels on a single polymeric card. Integrating 96 microwells in a single card does address the issues related to individually loading each sample cuvette into the thermal block. This approach does not, however, address the thermal cycling issues such as the high thermal mass of the metal block and heated cover or the relatively low thermal conductivity of the polymeric materials used to form the card. In addition, the thermal mass of the integrating card structure can extend thermal cycling times. Another potential problem of this approach is that if the card containing the sample wells is not seated precisely on the metal block, uneven well-to-well temperatures can be experienced, causing inaccurate test results.

Another problem experienced in the preparation of finished samples (e.g., isolated or purified samples of, e.g., nucleic acid materials such as DNA, RNA, etc.) of human, animal, plant, or bacterial origin from raw sample materials (e.g., blood, tissue, etc.) is the number of thermal processing steps and other methods that must be performed to obtain the desired end product (e.g., purified nucleic acid materials). In some cases, a number of different thermal processes must be performed, in addition to filtering and other process steps, to obtain the desired finished samples. In addition to suffering from the thermal control problems discussed above, all or some of these processes may require the attention of highly skilled professionals and/or expensive equipment. In addition, the time required to complete all of the different process steps may be days or weeks depending on the availability of personnel and/or equipment.

One example is in the preparation of a finished sample (e.g., purified nucleic acid materials) from a starting sample (e.g., a raw sample such as blood, bacterial lysate, etc.).

To obtain a purified sample of the desired materials in high concentrations, the starting sample must be prepared for, e.g., PCR, after which the PCR process is performed to obtain a desired common PCR reaction product. The common PCR reaction product must then be prepared for, e.g., Sanger sequencing, followed by performance of the Sanger sequencing process. Afterwards, the multiplexed Sanger sequencing product must be demultiplexed. After demultiplexing, the finished Sanger sequencing product is ready for further processing. This sequence of events may, however, have occurred over days or even weeks. In addition, the technical nature of the processes requires highly skilled personnel to obtain accurate results.

Approaches at using disc-based devices to integrate various thermal processing steps into a single device suffer from a number of disadvantages including the use of high cost silicon substrates and the incorporation of high cost heating and/or cooling systems built into the discs. As a result, the cost of the discs can be prohibitive to their widespread use. *See, e.g.,* International Publication Nos. WO 98/07019 (Kellog et al.); WO 99/09394 (Hubbard et al.).

## Summary of the Invention

The present invention provides devices and methods for thermal processing of sample materials. The sample materials may be located in a plurality of process chambers in the device which, in various aspects, may include one or more of: a reflective layer (e.g., a metallic layer); baffle structures to enhance cooling during rotation of the device; capture plugs to capture filtering materials; valve mechanisms capable of being selectively opened, thermal indicators for monitoring/controlling the temperatures in process chambers, absorptive materials in the process chambers to enhance energy absorption, etc. In various embodiments, the devices may include reagents, filters, and other sample processing materials in the process chambers. In other aspects, the present invention provides methods of using the devices to process sample materials and systems in which the devices may be used.

Significant advantages of the devices and methods of the present invention include the ability to perform complex thermal processing on sample materials in a manner that reduces variability of the results due to, e.g., human error. Further, with respect to the processing of biological materials for, e.g., genetic amplification, this advantage may be

achieved using operators that have a relatively low skill level as compared to currently used methods.

Among the thermal control advantages of the devices, methods and systems of the present invention are chamber-to-chamber temperature uniformity, comparable chamber-to-chamber temperature transition rates, and the increased speed at which thermal energy can be added or removed from the process chambers. Among the device features that can contribute to these thermal control advantages are the inclusion of a reflective layer (e.g., metallic) in the device, baffle structures to assist in removing thermal energy from the device, and low thermal mass of the device. By including thermal indicators in the devices, enhanced control over chamber temperature may be achieved even as the device is rotated during processing.

In those embodiments that include connected process chambers in which different processes may be sequentially performed on a starting sample, the present invention may provide an integrated solution to the need for obtaining a desired finished product from a starting sample even though multiple thermal processes are required to obtain the finished product.

In other embodiments in which the process chambers are multiplexed from a loading chamber (in which the starting sample is loaded), it may be possible to obtain multiple finished samples from a single starting sample. Those multiple finished samples may be the same materials where the multiplexed process chambers are designed to provide the same finished samples. Alternatively, the multiple finished samples may be different samples that are obtained from a single starting sample.

For those embodiments of the devices that include distribution channels formed in a metallic layer, the ductility of the metallic layer may provide a further advantage in that it may be possible to close or crush selected distribution channels to tailor the devices for specific test protocols, adjust for smaller sample material volumes, etc. It may also be advantageous to isolate the process chambers by closing or crushing the distribution channels after distributing sample materials to the process chambers.

For those embodiments that include a reflective layer forming a portion of each of the desired process chambers, the present invention may also provide the advantage of improved signal strength when the samples contained in the process chambers are

monitored for fluorescent or other electromagnetic energy signals. The signal strength may be improved if the reflective (e.g., metallic) layer reflects the electromagnetic energy being monitored as opposed to absorbing the energy or allowing it to be transmitted away from a detector. The signal strength may be even further improved if the metallic layer is formed into a shape that acts as a focusing reflector (e.g., parabolic reflector). If electromagnetic energy used to interrogate and/or heat materials in the process chambers is reflected by the reflective layer, then that layer may also improve the efficiency of the interrogation and/heating processes by effectively doubling the path length of the electromagnetic energy through the sample materials in the process chambers.

A further advantage of the embodiments of the invention that include a metallic layer is the relatively high strength to thickness ratio provided by the metallic layer. This may be particularly true when compared to devices that rely solely on polymeric materials to construct thermal processing devices. In addition to physical strength, the metallic layer may also provide beneficial barrier properties, i.e., a resistance to moisture vapor permeability. Another advantage that may also be provided by a metallic layer is its amenability to piercing without fracture to either introduce materials into, e.g., a loading port, or to remove materials, e.g., a finished sample, from a process chamber.

An advantage of those embodiments including filter chambers with capture plugs is that filtering material appropriate for the particular process being performed may be added at the point-of-use. For example, if the device is being used for genetic amplification, a filtering material designed to allow passage of nucleic acid materials of particular sizes may be delivered to the filter chamber before processing of the genetic materials.

Advantages of those embodiments including the valving mechanisms of the present invention include the ability to control movement of materials through the array of chambers and passageways present on the devices. A further advantage of the preferred valving mechanisms is that they do not contaminate the sample materials (as may, e.g., wax valves). Another advantage of the valving mechanisms may include the ability to selectively open the valves using, e.g., laser energy, while the devices are rotating during sample processing.

Advantages of those embodiments of the invention that include control patterns include the ability to control the delivery of electromagnetic energy to the device or other

functions, e.g., detection of changes in the process chambers, without requiring changes to the hardware and/or software used in the system employing the device. For example, the amount and/or wavelength of electromagnetic energy delivered to the process chambers and/or valves can be controlled using a control pattern on the device. Such control may further reduce the operator error associated with using the devices.

As used in connection with the present invention, "thermal processing" (and variations thereof) means controlling (e.g., maintaining, raising, or lowering) the temperature of sample materials to obtain desired reactions. As one form of thermal processing, "thermal cycling" (and variations thereof) means sequentially changing the temperature of sample materials between two or more temperature setpoints to obtain desired reactions. Thermal cycling may involve, e.g., cycling between lower and upper temperatures, cycling between lower, upper, and at least one intermediate temperature, etc.

These and other features and advantages of the devices, systems and methods of the invention are described below with respect to illustrative embodiments of the invention.

## BRIEF DESCRIPTION OF THE FIGURES

FIGURE 1 is a top plan view of one device according to the present invention.

FIGURE 2 is an enlarged partial cross-sectional view of a process chamber and distribution channel in the device of Figure 1.

FIGURE 3 is an enlarged partial cross-sectional view of an alternate device according to the present invention, illustrating a process chamber, distribution channel and a baffle structure.

FIGURE 4 is a plan view of one major side of the device of Figure 3.

FIGURE 5 is an enlarged partial cross-sectional view of a process chamber and distribution channel in the device of Figure 3 after isolation of the process chamber.

FIGURE 6 is a perspective view of a portion of one edge of another alternative device according to the present invention.

FIGURE 7 is a plan view of a portion of the device of Figure 6 including a process chamber, a distribution channel and baffles.

FIGURE 8 is a cross-sectional view taken along line 8-8 in Figure 7.

FIGURE 9 is a schematic diagram of one thermal processing system according to the present invention.

FIGURE 10 is partial cross-sectional view of another device according to the present invention.

FIGURE 11 is a partial cross-sectional view of another device according to the present invention.

FIGURE 12 is a schematic diagram of another thermal processing system according to the present invention.

FIGURE 13 is a partial cross-sectional view of another device according to the present invention taken along line 13-13 in Figure 14.

FIGURE 14 is a plan view of one surface of a device according to the present invention.

FIGURE 15 is a partial cross-sectional view of the device of Figures 13 and 14 taken along line 15-15 in Figure 16.

FIGURE 16 is a plan view of another surface of the device of Figures 13-15.

FIGURE 17 is a schematic diagram of one structure that may be used to provide integrated processing of starting sample materials by, e.g., PCR amplification and Sanger sequencing on a single device.

FIGURE 18 is a plan view of one major surface of a device according to the present invention.

FIGURE 19 is a cross-sectional view of the device of Figure 18 taken along line 19-19 in Figure 18.

FIGURE 20 is a plan view of the other major surface of the device of Figure 18, depicting a control pattern provided on the device.

FIGURE 21 is a cross-sectional view of another device according to the present invention.

FIGURE 22 is a cross-sectional view of the device of Figure 21 after opening of one of the valves in the device.

## Detailed Description Of Illustrative Embodiments Of The Invention

The present invention provides a device that can be used in methods that involve thermal processing, e.g., sensitive chemical processes such as PCR amplification, ligase chain reaction (LCR), self-sustaining sequence replication, enzyme kinetic studies, homogeneous ligand binding assays, and more complex biochemical or other processes that require precise thermal control and/or rapid thermal variations. The device may include, e.g., a reflective layer, baffle structures, valve mechanisms, capture plugs, thermal indicators, absorptive materials, and other materials or components that facilitate rapid and accurate thermal processing of sample materials in the process chambers of the device.

One illustrative device manufactured according to the principles of the present invention is illustrated in Figures 1 and 2. The device 10 is preferably in the shape of a circular disc as illustrated in Figure 1, although any other shape that can be rotated could be used in place of the preferred circular disc. The device 10 of Figures 1 and 2 is a multi-layered composite structure including a substrate 20, first layer 30, and a second layer 40.

The device 10 includes a plurality of process chambers 50, each of which defines a volume for containing a sample and any other materials that are to be thermally cycled with the sample. The illustrated device 10 includes ninety-six process chambers 50, although it will be understood that the exact number of process chambers provided in connection with a device manufactured according to the present invention may be greater than or less then ninety-six, as desired.

The process chambers 50 in the illustrative device 10 are in the form of chambers, although the process chambers in devices of the present invention may be provided in the form of capillaries, passageways, channels, grooves, or any other suitably defined volume.

It is preferred that the substrate 20, first layer 30 and second layer 40 of the device 10 be attached or bonded together with sufficient strength to resist the expansive forces that may develop within the process chambers 50 as, e.g., the constituents located therein are rapidly heated during thermal processing. The robustness of the bonds between the components may be particularly important if the device 10 is to be used for thermal cycling processes, e.g., PCR amplification. The repetitive heating and cooling involved in such thermal cycling may pose more severe demands on the bond between the sides of the device 10. Another potential issue addressed by a more robust bond between the

components is differences in the coefficients of thermal expansion of the different materials used to manufacture the components.

Also disclosed in Figure 2 is a reagent 52 located within the process chamber 50. The reagent 52 may preferably be fixed to a surface of the process chamber 50. The reagent 52 is optional, i.e., some devices 10 may or may not include any reagents 52 loaded in the process chambers 50. In another variation, some of the process chambers 50 may include a reagent 52 while others do not. In yet another variation, different process chambers 50 may contain different reagents.

The illustrated device 10 also includes an optional registration system whereby the position of the different process chambers 50 can be accurately determined, even as the device 10 is rotated during the processing methods described in more detail below. The registration system may be provided in the form of registration marks 14 on the device 10. Another alternative registration system may involve keying the device 10 such that it can be mounted on, e.g., a rotating spindle, in only one orientation. In such a system, the rotational position of the spindle would then be indicative of the position of the various features on the device 10. Other registration systems will be known to those skilled in the art.

The process chambers 50 are in fluid communication with distribution channels 60 that, together with loading port 62, provide a distribution system for distributing samples to the process chambers 50. Introduction of samples into the device 10 through the loading port 62 may be accomplished by rotating the device 10 about a central axis of rotation such that the sample materials are moved outwardly due to centrifugal forces generated during rotation. Before the device 10 is rotated, the sample can be introduced into the loading port 62 for delivery to the process chambers 50 through distribution channels 60. The process chambers 50 and/or distribution channels 60 may include ports through which air can escape and/or other features to assist in distribution of the sample materials to the process chambers 50. Alternatively, it may be possible to provide a closed distribution system, i.e., a system in which materials may be introduced through an opening through which air within the process chambers 50 and/or distribution channels 60 also escapes during the distribution process. In another alternative, sample materials could be loaded into the process chambers 50 under the assistance of vacuum or pressure.

The distribution channel 60 illustrated in Figure 2 is formed in the substrate 20 of the illustrative device 10. The channel 60 is in fluid communication with the process chamber 50 and is also in fluid communication with the loading port 62. The channel 60 may be formed by a variety of techniques, preferably a microreplication technique. Examples of suitable microreplication techniques include micromilling, injection molding, vacuum molding, laser ablation, photolithography, thermoforming, embossing, etc.

The illustrated device 10 includes a loading port 62 with two chambers 64 that are isolated from each other. As a result, a different sample can be introduced into each chamber 64 for loading into the process chambers 50 that are in fluid communication with the respective chamber 64 of the loading port 62 through distribution channels 60. It will be understood that the loading port 62 may contain only one chamber or that any desired number of chambers 64, i.e., two or more chambers 64, could be provided in connection with the device 10.

Figure 2 is an enlarged cross-sectional view of a portion of the device 10 including one of the process chambers 50 and a distribution channel 60. The substrate 20 includes a first major side 22 and a second major side 24. Each of the process chambers 50 is formed, at least in part in this embodiment, by a void 26 formed through the substrate 20. The illustrated void 26 is formed through the first and second major sides 22 and 24 of the substrate 20.

The substrate 20 is preferably polymeric, but may be made of other materials such as glass, silicon, quartz, ceramics, etc. Furthermore, although the substrate 20 is depicted as a homogenous, one-piece integral body, it may alternatively be provided as a non-homogenous body of, e.g., layers of the same or different materials. For those devices 10 in which the substrate 20 will be in direct contact with the sample materials, it may be preferred that the material or materials used for the substrate 20 be non-reactive with the sample materials. Examples of some suitable polymeric materials that could be used for the substrate in many different bioanalytical applications include, but are not limited to, polycarbonate, polypropylene (e.g., isotactic polypropylene), polyethylene, polyester, etc.

A first layer 30 is provided on one side of the substrate 20 in the illustrated embodiment and preferably includes a metallic sub-layer 34 located between an optional passivation layer 32 and an optional outer protective layer 36. The first layer 30 thus

defines a portion of the volume of the process chamber 50. A second layer 40 is provided on the opposite side of the substrate 20 to define the remainder of the volume of the process chamber 50.

It may be preferred that at least a portion of the materials defining the volume of the process chamber 50 be transmissive to electromagnetic energy of selected wavelengths. The selected wavelengths may be determined by a variety of factors, for example, electromagnetic energy designed to heat and/or interrogate a sample in the process chamber 50, electromagnetic energy emitted by the sample (e.g., fluorescence), etc.

In the device 10, where the first layer 30 includes a metallic sub-layer 34, it may be preferred that the materials used for the second layer 40 of the device 10 transmit electromagnetic energy of selected wavelengths. By providing a transmissive process chamber 50, a sample in the chamber can be interrogated by electromagnetic energy of selected wavelengths (if desired) and/or electromagnetic energy of the selected wavelengths emanating from the sample can be transmitted out of the process chamber 50 where it can be detected by suitable techniques and equipment. For example, electromagnetic energy may be emitted spontaneously or in response to external excitation. A transmissive process chamber 50 may also be monitored using other detection techniques, such as color changes or other indicators of activity or changes within the process chambers 50.

In the device illustrated in Figure 2, the first layer 30 preferably includes a structure such that the first layer 30 deviates from an otherwise flat surface on at least the surface 37 facing the interior volume of the process chamber 50. For example, the first layer 30 may be cast, molded, thermoformed, embossed or otherwise manufactured to produce an interior surface 37 that has a desired shape. The shape of the structure formed in the first layer 30 may vary, although it may be preferred that the shape of the interior surface 37 facing the volume of the process chamber 50 be concave (e.g., parabolic) such that some focusing of any electromagnetic energy reflected from that surface may be effected.

It may also be preferred that the exterior surface of the first layer 30, i.e., the surface that faces away from the substrate 20, also include baffle structure 38 such that airflow is disrupted over the first layer 30 as the device 10 is rotated. By disrupting airflow over the first layer 30, heat transfer of energy out of the first layer 30 into the

surrounding atmosphere may be enhanced. The illustrated first layer 30 includes a baffle structure 38 with a shape that corresponds to the shape of the interior surface 37 of the metallic sub-layer 34, although the shape of the baffle structure 38 may alternatively be different than the shape of the interior surface 37.

The metallic sub-layer 34 is preferably not exposed to the interior volume of the process chamber 50 to prevent contamination of any sample by the metal or metals used in the metallic sub-layer 34. The optional passivation layer 32 is provided to prevent exposure of the metallic sub-layer 34 to the interior volume of the process chamber 50. The materials used in the passivation layer 32 are preferably capable of secure attachment to both the metallic sub-layer 34 and the materials used in for the substrate 20 by, e.g., adhesives, heat sealing, etc. It is also preferred that the materials used for the passivation layer 32 be non-reactive with any materials in the samples located within the process chambers 50. Examples of suitable materials for the passivation layer 32 may include, but are not limited to, polypropylene (e.g., isotactic polypropylene), polyethylene, polyester, etc.

Although the passivation layer 32 is depicted as a single homogenous structure, it may be formed as two or more layers of the same or different materials. For example, an adhesion promoting layer may be used to enhance adhesion of the passivation layer 32 to, e.g., the metallic sub-layer 34. The adhesion promoting layer may be, e.g., heat-sealable, a pressure sensitive adhesive, hot melt adhesive, curable adhesive, etc.

Further, although the passivation layer 32 is preferably substantially coextensive with the metallic sub-layer 34, the passivation layer 32 may be provided in a discontinuous pattern on the metallic sub-layer 34, with the discontinuous pattern preventing exposure of the metallic sub-layer 34 to the interiors of the process chambers 50.

The materials and/or thickness of the passivation layer 32 may also preferably be selected to transmit electromagnetic energy of selected wavelengths to allow for reflection from the underlying metallic sub-layer 34 without significant absorption or diffusion. This may be particularly true where the shape of the interior surface of the metallic sub-layer 34 is designed to provide some focusing of electromagnetic energy. It may also be preferred that the passivation layer 32 be relatively thin so that the transfer of thermal energy from any sample materials in the process chambers 50 into the metallic sub-layer 34 is not

substantially inhibited (so that energy can be dissipated into the atmosphere or another structure). For example, where the passivation layer 32 is an isotactic polypropylene, the layer 32 may preferably be about 0.005 inches (0.13 mm) or less, more preferably about 0.002 inches (0.05 mm) or less.

The metallic sub-layer 34 may take a variety of forms. Although the layer 34 is depicted as a single, homogenous structure, it may be provided as a multi-layer structure of two or more layers. It may be preferred that the metallic sub-layer 34 consist essentially of one or more metals. Examples of suitable metals that could be used in the metallic sub-layer 34 include aluminum, stainless steel, copper, titanium, silver, gold, tin, etc. One potential advantage of a metallic sub-layer 34 is that the metallic layer may assist in equilibrating the temperature between process chambers 50 by conducting heat away from hot spots or into cool spots on the device 10.

The thickness of the layer 34 may be selected to provide a relatively low thermal mass to facilitate rapid thermal cycling of the samples in the process chambers 50. The desire for low thermal mass of the metallic sub-layer 34 may, however, be balanced by a number of factors.

For example, the desire for a metallic sub-layer 34 with low thermal mass may be balanced by a desire for thermal conductivity across the device 10, e.g., between chambers 50. That thermal conductivity across the device 10 can contribute to chamber-to-chamber temperature uniformity, as well as comparable chamber-to-chamber temperature transition rate.

Another factor to balance with the desire for reduced thermal mass is the need for integrity of the first layer 30. In many devices 10, the metallic sub-layer 34 may provide a significant portion, or even a majority, of the structural integrity of the first layer 30. A metallic sub-layer 34 that is too thin or manufactured of the wrong metal or metals may not provide sufficient integrity for the device 10. For example, if the metallic sub-layer 34 is to be formed (e.g., stamped, etc.) to assist in the formation of the process chambers 50, distribution channels (*see, e.g.,* Figure 3), baffle structure 38, etc., the metal or metals and their thickness should be amenable to such processes.

The barrier properties of the metal or metals and their thickness used in the metallic sub-layer 34 may also need to be balanced against the desire for reduced thermal

mass. For example, the metallic sub-layer 34 may need to be thick enough to provide sufficient vapor barrier properties in response to the thermal processing taking place in the process chambers 50 or to increase the shelf-life of the device 10 where, e.g., moisture sensitive reagents 52 are pre-loaded within the process chambers 50.

Yet another factor to consider when selecting the thickness of the metallic sub-layer 34 and the metal or metals in it may be the need for reflectivity. If the metallic sub-layer is too thin and/or formed of the wrong metals, it may not exhibit sufficient reflectivity over the selected wavelengths of electromagnetic energy.

When balancing all of the concerns discussed above, it may be preferred that the thickness of the metallic sub-layer 34 be about 0.04 inches (1 mm) or less, more preferably about 0.02 inches (0.5 mm) or less, and still more preferably about 0.010 inches (0.25 mm) or less. At the lower end of the range, the thickness of the metallic sub-layer 34 may preferably be sufficient to provide the desired reflectivity and/or structural integrity to the first layer 30 of the device 10. For example, it may be preferred that the metallic sub-layer 34 be at least about 0.0005 inches (0.013 mm) thick, more preferably at least about 0.001 inches (0.025 mm) thick, and still more preferably about 0.003 inches (0.075 mm).

The actual range of suitable thickness for the metallic sub-layer 34 may depend, at least in part, on the thermal properties of the metal or metals used to form the layer. Where the layer 34 is formed of aluminum, the layer 34 may preferably have a thickness in the range of, e.g., about 0.025 millimeters (mm) to about 0.25 mm.

As an alternative, the reflective properties desired in the devices of the present invention may be provided by non-metallic reflective materials. For example, multi-layer polymeric films may be used to provide the desired reflectivity or to enhance the reflectivity of metallic layers used in the devices of the present invention. Reflective polymeric films that may be useful in connection with the present invention are described in U.S. Patent No. 5,882,774 (Jonza et al.); U.S. Patent Application Serial No. 08/479,319, filed June 7, 1995; U.S. Patent Application Serial No. 09/006,455; and International Publication Nos. WO 99/36809, WO 99/36810, WO 99/36248, and WO 99/36258.

Also depicted in Figure 2 is an optional protective layer 36 provided on the surface of the metallic sub-layer 34 that faces away from the process chamber 50. The protective layer 36 may protect the integrity of the metallic sub-layer 34 and/or may increase the

toughness of the device 10. Another potential advantage of the protective layer 36 is the reduction or prevention of oxidation of the metallic sub-layer 34 (which could adversely affect the rate of thermal energy transfer out of the metallic sub-layer 34).

Still another advantage of providing both an outer protective layer on one side of a metallic sub-layer and a passivation layer on the other side of the metallic layer is that the formability of the first layer 30 may be improved. If, for example, a side of the device including a metallic sub-layer 34 is to be formed to provide process chambers (*see, e.g.,* Figure 3), distribution channels, baffle structures, or any other features, the formability of the side including the metallic sub-layer may be improved if the metallic sub-layer is covered on both sides. This may be especially true with forming processes that involve molding (e.g., plug molding, vacuum molding, thermoforming, etc.).

The thickness and the materials used for the protective layer 36 are preferably such that the layer 36 does not substantially affect the transfer of thermal energy out of the metallic sub-layer 34. An example of one suitable protective layer 36 is a thin coating of epoxy with a thickness of about 0.001 inches (0.025 mm). Other examples of non-metallic protective layer materials include, but are not limited to, polyester, polycarbonate, polypropylene, polyethylene, etc.

One product that may meet many of the above criteria for the first layer 30 is a heat sealing metal foil available from Marsh Biomedical Products, Inc., Rochester New York under the designation AB-0559.

Figure 3 is an enlarged partial cross-sectional view of another illustrative embodiment of a device 110 according to the present invention, the second layer 140 of which is illustrated in the plan view provided in Figure 4. The device 110 includes a substrate 120, first layer 130 and second layer 140 constructed in much the same manner as the device 10 described above. It should be noted that the first layer 130 of the device 110 does not include the optional outer protective layer of device 10, but is preferably constructed of a passivation layer 132 and a metallic sub-layer 134.

Among the other differences between the device 10 and device 110 are that the distribution channel 160 that is in fluid communication with the process chamber 150 is formed primarily as a structure in the first layer 130. The structure required to form the channel 160 in the first layer 130 can also provide a baffle structure 138 on the bottom of

the device 110. The baffles 138 formed in the bottom layer 130 could take on the form of the distribution channels 160 required to distribute sample materials to the process chambers 150. One example such a pattern is illustrated by the channels 60 in Figure 1.

Another difference is that the second layer 140 may also include baffle structures 142 designed to increase the turbulence in airflow over the device 110 as it is rotated. The baffles 142 are seen in Figures 3 and 4. Although the illustrated baffles 142 on the cover layer 140 are arranged radially on the device 110, it will be recognized that they could be provided in any pattern designed to increase turbulent flow or other flow that improves heat transfer out of the device 110. The baffles 142 may be integral with the second layer 140 or they may be provided as separate articles adhered or otherwise attached to the second layer 140.

Figure 5 is another enlarged partial cross-sectional view of the device 110 of Figures 3 and 4. This figure illustrates one technique for sealing or isolating the process chamber 150 to, e.g., prevent cross-contamination or diffusion between process chambers 150 in the device 110 after the process chambers 150 have been loaded with sample material. The illustrated technique involves closing the channel 160 by compressing the first layer 130 against the substrate 120. The sealing of the channel 160 may be accomplished mechanically, i.e., by simply crushing the channel 160, or it may be accompanied by the application of heat to enhance adhesion of the first layer 130 to the substrate 120. Alternatively, sufficient isolation may be achieved by continuously rotating the device during processing, such that the sample materials are retained in the process chambers by centrifugal forces.

The sealing of distribution channels may be performed for a variety of purposes in addition to isolating process chambers after distribution of sample materials. For example, selected distribution channels may be sealed before distribution of sample material to reduce the volume of sample material needed to fill the process chambers that remain in fluid communication with the distribution system. In another approach, the tests to be performed using the devices may be customized by sealing selected distribution channels before distributing the sample materials into the process chambers.

Figures 6-8 depict yet another illustrative embodiment of a device 210 manufactured according to the present invention. The device 210 includes a substrate 220,

first layer 230 and second layer 240. Figure 6, a perspective view of a portion of one edge of the device 210, illustrates a baffle 238 provided in the first layer 230 and a baffle 242 in the second layer 240. As a result, both major sides of the device 210 include at least one baffle, preferably two or more baffles, to increase turbulent flow over those surfaces.

Referring to Figure 7, a plan view of a portion of the device 210 including a process chamber 250 and a distribution channel 260 in fluid communication with the process chamber 250. Figure 8 is a cross-sectional view taken along line 8-8 in Figure 7, and illustrates the process chamber 250 and distribution channel 260, both of which are formed in the substrate 220 by any suitable technique, preferably a microreplication technique. Examples of suitable microreplication techniques include micromilling, injection molding, vacuum molding, laser ablation, photolithography, thermoforming, embossing, etc. The process chamber 250 is formed primarily by a void formed through the substrate 220. Alternatively, the process chamber 250 may be formed by a depression formed through only a portion of the thickness of the substrate 220.

The first layer 230 of the device 210 may or may not include any metals or metallic sub-layers as discussed in connection with the devices 10 and 110 above. Also illustrated in Figure 8 are a baffle 238 on the first layer 230 and a baffle 242 on the second layer 240.

One illustrative system for accomplishing a thermal cycling process using a device according to the present invention is schematically depicted in Figure 9. The system 300 includes a device 310 located on a spindle 314 that rotates the device about an axis 312. The device includes process chambers 350 into which a sample material is distributed by, e.g., distribution channels as discussed above or any other suitable techniques and/or structures.

After distribution of the sample material into the process chambers, individual chambers 350 can be selectively heated by suitable electromagnetic energy supplied by an electromagnetic energy source 370 that heats the materials in the process chambers 350. The electromagnetic energy source 370 is preferably remote from the device 310, i.e., it is not located on the device 310. Examples of some suitable electromagnetic energy sources may include, but are not limited to, lasers, broadband electromagnetic energy sources (e.g., white light), etc. The electromagnetic energy source 370 may be provided continuously or intermittently based on a variety of factors, e.g., the desired temperature of the sample

materials, the rate at which thermal energy is removed from each process chamber, the desired rate of temperature change, whether the process chambers include a reflective component, etc. If the electromagnetic energy source 370 is cycled or otherwise varied, the registration system discussed above may be used to deliver a selected amount of energy to selected process chambers.

As the device 310 rotates, it is preferred that the airflow over the surface of the device 310 assists in cooling the sample materials in the process chambers 350 to a selected base temperature from the upper target temperature to which the sample materials are heated by the electromagnetic energy from the source 370. In some systems, one or both surfaces of the device 310 may be exposed to the atmosphere to also assist in cooling. The system 300, however, includes an optional base plate 380 that is itself held at a lower temperature. By holding the bottom of the device 310 in contact with the base plate 380, it may be possible to assist in cooling the sample materials in the process chambers 350 between heating cycles as the device 310 rotates during processing. If a base plate 380 is used to assist in thermal control, it may be helpful to use a device 310 incorporating a metallic layer proximate the base plate 380 to improve thermal conductivity between the base plate and the device 310.

Figure 9 also includes an optional additional temperature control mechanism in the form of a fluid source 382, e.g., pressurized air or any other suitable fluid, that can be directed at the surface of the device 310. The fluid used can be either heated or cooled to a desired temperature. Where it is desired to cycle the sample materials between upper and lower temperatures, the fluid may be provided at the lower temperature. Although depicted as being directed at only one surface of the device 310, it will be understood that the fluid may be directed at both surfaces of the device if desired.

The system 300 may also include various other components such as a detection system 390 provided to detect the results of processing of the sample materials in the process chambers 350. For example, the detection system and method may involve active interrogation of the process chambers 350 to detect fluorescent reaction products in the chambers as the device 310 rotates. The detection may be qualitative or quantitative. Other detection systems may be provided to monitor, e.g., the temperatures or other properties of the materials in the process chambers 350.

As the thermal cycling method is performed, the temperature within the process chambers 350 may be monitored to control the application of energy into the chambers 350. Among the variables that may be manipulated to control the sample material temperatures in the device 310 include the intensity of the laser or other light source, the rotational speed of the device 310 (which can affect the cooling rate and the dwell time of each of the process chambers in the laser or other light source), the temperature of the base plate 380, and the temperature and pressure of the fluid source 382.

Referring now to Figure 10, which depicts a partial cross-sectional view of an alternative device 410 according to the present invention, temperature sensing materials 454 may be located within the process chambers 450 of the device 410. Among the potential temperature sensing materials 454 are structures that incorporate thermochromic dyes, temperature-sensitive fluorescent materials, etc. It may be desirable that these materials be in direct contact with any sample materials in the process chambers 450 and, in the illustrated embodiment, the temperature sensing material 454 surrounds at least a portion of the process chamber 450. Many other structures and techniques for providing such temperature sensing materials 454 may, however, be substituted for that illustrated in Figure 10. For example a portion of the substrate 420 or the first layer 430 may be doped or coated with a temperature sensing material.

Figure 11 illustrates another device 510 (in a partial cross-sectional view) according to the present invention in which electromagnetic energy receptive materials 556 are used. It may be desirable that the electromagnetic energy receptive materials 556 be in direct contact with any sample materials in the process chambers 550 and, in the illustrated embodiment, the electromagnetic energy receptive materials 556 surround at least a portion of the process chamber 550. Many other structures and techniques for providing electromagnetic energy receptive materials 556 may, however, be substituted for that illustrated in Figure 11. For example a portion of the substrate 520 or the first layer 530 may be coated with an electromagnetic energy receptive material.

The electromagnetic energy receptive material 556 can take a variety of forms, provided that is capable of converting electromagnetic radiation in one form or another to thermal energy. That thermal energy can then be communicated to the sample materials in the process chambers 550 by, e.g., conduction. Examples of some suitable materials may

include those described in U.S. Patent Nos. 5,278,377 (Tsai); 5,446,270 (Chamberlain et al.); 5,529,708 (Palmgren et al.); and 5,925,455 (Bruzzone et al.).

The advantage of using an electromagnetic energy receptive material 556 is that the sample materials in the device 510 can be heated in the absence of physical contact with the device 510. For example, if the electromagnetic energy receptive material 556 is sensitive to radio-frequency (RF) radiation, the device 510 can be rotated such that the process chambers 550 are resident within an RF field for sufficient time to obtain the desired heating. Similar non-contact heating may be obtained with microwave radiation, etc. It will, however, be understood that the form in which the electromagnetic radiation is provided should be compatible with the sample materials located within the process chambers 550.

Figure 12 schematically illustrates another system 500 in which device 510 is located on a spindle 514 that rotates the device about an axis 512. The device 510 includes process chambers 550 into which a sample material is distributed by, e.g., distribution channels as discussed above or any other suitable techniques and/or structures.

After distribution of the sample material into the process chambers, individual chambers 550 can be selectively heated by suitable electromagnetic energy, e.g., RF, microwave, etc., supplied by an electromagnetic energy source 570 to heat electromagnetic energy receptive materials in the device 510. The electromagnetic energy receptive materials can then communicate the thermal energy to sample materials in the process chambers 550. The electromagnetic energy source 570 may be provided continuously or intermittently as discussed above with respect to the system 300 above. Various cooling and detection mechanisms such as those discussed in connection with system 300 (see Figure 9) may also be incorporated into system 500.

Figures 13-16 illustrate another embodiment of a device in accord with the present invention. Portions of the device 610 are depicted in a variety of plan and partial cross-sectional views. Generally, the device 610 may preferably be in the form of a disc similar to that seen in, e.g., Figure 1. The device 610 includes a core 620 in which a variety of structures are formed. A first cover layer 630 is attached to a first major side 622 of the core 620 and a second cover layer 640 is attached to a second major side 624 of the core 620. Figures 13-16 illustrate one set of interconnected process chambers and other

features that may be replicated a number of times around the device 610 in a manner similar to the process chambers 50 arrayed about device 10 in Figure 1. Each set of interconnected process chambers and other features can be described as forming a process chamber array, with a number of the arrays arranged generally radially about the device 610.

Figure 13 is a partial cross-sectional view of a portion of the device 610 including one of the process chamber arrays that is taken along line 13-13 in Figure 14, which is a plan view of the second major side 624 of the core 620 with the second cover layer 640 removed. Figure 15 is a partial cross-sectional view of a portion of the device 610 taken along line 15-15 in Figure 16, which is a plan view of the first major side 622 of the core 620 with the first cover layer 640 removed.

The first cover layer 630 may include multiple sub-layers 632, 634, and 636 in the various constructions described above. It may be preferred that the first cover layer 630 include a reflective sub-layer (e.g., metallic, polymeric, etc.) as discussed in the embodiments described above. The second cover layer 640 may include, e.g., an adhesive 642 and a substrate 644, both of which may be optically clear or otherwise transmissive to electromagnetic energy of selected wavelengths.

Among the features formed in the core 620 are a loading chamber 662a that, in the illustrated embodiment, is in the form of an annular ring (only a portion of which is seen in Figures 13-16). The loading chamber 662a is in fluid communication with a first or inner process chamber 650a through a channel 660a. It will typically be preferred that the loading chamber 662a be located closer to the center of the device 610 than the inner process chamber 650a such that rotation of the device 610 about its center causes materials located in the loading chamber 662a to move towards inner process chamber 650a through channel 660a.

The core 620 also includes features formed in the first major surface 622, such as intermediate process chamber 650b, which may be another chamber in which materials are thermally processed. Alternatively, the intermediate process chamber 650b may be provided to perform another function, e.g., filter materials delivered to it from inner process chamber 650a. The intermediate process chamber 650b may be in fluid

communication with a second loading chamber 662b through channel 660b that, in the illustrated embodiment, is formed in the first major surface 622 of the core 620.

The inner process chamber 650a and intermediate process chamber 650b are connected by a channel 660c and a via 660d. The channel 660c extends from the inner process chamber 650a to the via 660d which, in turn, extends to the intermediate process chamber 650b. The channel 660c and/or via 660d may preferably include a valve mechanism if precise control over the movement of materials between the inner process chamber 650a and intermediate process chamber 650b is desired. The valve mechanism may take a number of forms, e.g., thermal plugs (e.g., waxes, etc.) or other structures that can be opened when desired. Alternatively, the valving may be provided by varying the rotational speed of the disc to overcome the resistance of materials to move through the channel 660c and/or via 660d.

The intermediate process chamber 650b is also connected to the outer process chamber 650c by a via 660e and channel 660f in a manner similar to that used to connect inner process chamber 650a and intermediate process chamber 650b. The via 660e and/or channel 660f may also include a valve mechanism if so desired.

It is preferred that the process chamber array including chambers 650a, 650b, and 650c be arranged generally radially from the center of the device 610, i.e., the point about which the device is rotated. As a result, rotation of the device 610 can be used to move materials successively from inner process chamber 650a to intermediate process chamber 650b and, finally, to outer process chamber 650c. By moving the materials through the process chambers as desired, selected processes can be performed sequentially within the process chamber array on the device 610.

It may be desired that the channels and vias in the device 610 may also include filters or other structures/materials needed to perform functions. For example, a porous capture plug 670 may be located within the via 660e. The porous capture plug 670 may advantageously capture filter materials moving from the loading chamber 662b to the intermediate process chamber 650b. For example, it may be desirable to dispense filtering material in the form of, e.g., beaded size exclusion substances. Such materials may be entrained within a fluid when supplied to the loading chamber 662b. When the device 610 is rotated, the entrained beads may be driven to the intermediate process chamber 650b

through channel 660b. The porous capture plug 670 in via 660e allows the fluid carrying the beads to pass but prevents the beads from passing, thereby capturing them within the process chamber 650b.

A particular advantage of the porous capture plug 670 used to capture filtering material within process chamber 650b is that the filter material dispensed to the chamber 650b may be selected at the point-of-use based on the characteristics of the sample materials being processed. Where the filtering material dispensed to the chamber 650b is, e.g., size exclusion beads, the properties of the beads may be selected to, e.g., remove the typically shorter PCR primers while allowing the typically longer PCR products to pass through to the outer process chamber 650c. The sizes of the primers and the PCR products may vary in each application and the ability to select the appropriate size exclusion material for process chamber 650b may be particularly advantageous.

The various devices, systems and methods described above can be used in a variety of different processes requiring thermal cycling of samples contained in the process chambers of the devices. Examples of some such processes involve chemical reactions on samples, e.g., nucleic acid amplification. For example, samples may be mixed with a polynucleotide, a polymerase (such as *Taq* polymerase), nucleoside triphosphates, a first primer hybridizable with the sample polynucleotide, and a second primer hybridizable with a sequence complementary to the polynucleotide. Some or all of the required reagents may be present in the device as manufactured, they may be loaded into the process chambers after manufacture of the device, they may be loaded in the process chambers just before introduction of the sample, or they may be mixed with sample before loading into the process chambers.

Although polynucleotide amplification by PCR is described in the most detail herein, the devices and methods of using them may be used for a variety of other polynucleotide amplification reactions and ligand-binding assays. The additional reactions may be thermally cycled between alternating upper and lower temperatures, such as PCR, or they may be carried out at a single temperature, e.g., nucleic acid sequence-based amplification (NASBA). The reactions can use a variety of amplification reagents and enzymes, including DNA ligase, T7 RNA polymerase and/or reverse transcriptase, etc. Polynucleotide amplification reactions that may be performed using the devices and/or

methods of the invention include, but are not limited to: a) target polynucleotide amplification methods such as self-sustained sequence replication (3SR) and strand-displacement amplification (SDA); b) methods based on amplification of a signal attached to the target polynucleotide, such as "branched chain" DNA amplification; c) methods based on amplification of probe DNA, such as ligase chain reaction (LCR) and QB replicase amplification (QBR); d) transcription-based methods, such as ligation activated transcription (LAT) and nucleic acid sequence-based amplification (NASBA); and e) various other amplification methods, such as repair chain reaction (RCR) and cycling probe reaction (CPR).

In addition to genetic amplification methods, other chemical or biochemical reaction applications may also be performed using the devices and/or methods of the invention. For example, temperature controlled lysis of cells may or may not be practiced in connection with the amplification processes discussed above. Furthermore, the devices and methods may be used to control and interrogate chemical reactions. By rapidly transitioning between desired temperatures, unwanted side reactions that occur at intermediate temperatures can be reduced or eliminated, potentially increasing measurement accuracy and improving product purity. Other applications other than those discussed herein may also benefit from the devices and methods of the present invention.

Of the potential uses for the devices and methods of the present invention, PCR is one important such use and methods of using the devices in connection with PCR will now be briefly described, although it should be understood that the present invention is not limited to PCR amplification.

PCR allows for analysis of extremely small amounts of nucleic acid (e.g., DNA). Briefly, a nucleic acid molecule is repeatedly synthesized using a polymerase enzyme, which results in the amplification of a particular sequence – by a millionfold or more. Specifically, PCR amplification involves separating two strands of nucleic acid (i.e., denaturing) under high temperature conditions. An excess of two oligonucleotide primers are used that are capable of flanking the region to be amplified. These primers hybridize to the denatured target nucleic acid molecule and extend the nucleic acid molecule by nucleotide addition from the primers by the action of a polymerase enzyme. The target molecule is defined by 3'- and 5'-flanking nucleic acid portions to which oligonucleotide

primers are annealed. The primers are then extended across the target nucleic acid molecule by using a heat-stable polymerase (such as *Taq* DNA polymerase) in the presence of free deoxynucleoside triphosphates (dNTPs), resulting in a double replication of the starting target nucleic acid molecule. The nucleic acid molecules are again thermally treated to denature, and the process is repeated.

"Primer" refers to an oligonucleotide, whether occurring naturally as in a purified restriction digest or produced synthetically, which is capable of acting as a point of initiation of synthesis when placed under conditions in which synthesis of a primer extension product that is complementary to a target nucleic acid strand is induced, i.e., in the presence of nucleotides and an agent for polymerization (such as a DNA polymerase) and at a suitable temperature and pH. The primer is preferably single stranded for maximum efficiency in amplification. Preferably, the primer is an oligodeoxyribonucleotide. The primer must be sufficiently long to prime the synthesis of extension products (referred to herein as "PCR products" and "PCR amplicons") in the presence of the polymerization agent. Primers are preferably selected to be "substantially" complementary to a portion of the target nucleic acid sequence to be amplified. This typically means that the primer must be sufficiently complementary to hybridize with its respective portion of the target sequence. For example, a primer may include a non-complementary nucleotide portion at the 5' end of the primer, with the remainder of the primer being complementary to a portion of the target sequence. Alternatively, non-complementary bases or longer sequences can be interspersed into the primer, provided that the primer sequence has sufficient complementarity with a portion of the target sequence to hybridize therewith, and thereby form a template for synthesis of the extension product.

Preferably, PCR amplification generates PCR amplification products (also referred to as PCR amplicons) incorporating a detectable label or tag. Thus, PCR amplification of target nucleic acid is preferably accomplished by utilizing at least one primer containing a detectable tag. For example, ultraviolet, visible, or infrared absorbing tags could be used that would produce specific ultraviolet, visible, or infrared signals. Examples of a wide variety of tags (a chemical moiety that is used to uniquely identify a nucleic acid of interest) are disclosed in International Publication No. 97/27325.

Particularly preferred such tags are fluorescent agents. These are typically dye compounds that emit visible radiation in passing from a higher to a lower electronic state, typically in which the time interval between adsorption and emission of energy is relatively short, generally on the order of about $10^{-8}$ to about $10^{-3}$ second. Suitable fluorescent compounds can include fluorescein, rhodamine, luciferin, as chamber as a wide variety of others known to one of skill in the art (see, for example, the list of dyes available on the world wide web at "www.apbiotech.com/product/product_index.html" or "www.pebio.com" or "www.probes.com").

As used in the devices of the present invention, it may be advantageous to provide DNA primers and probes in the process chambers during manufacturing of the devices. A DNA target sample could then be introduced into the process chambers to conduct PCR amplification of the DNA target. The target sample may include, e.g., target DNA, buffer and polymerase enzyme.

After the target sample has been distributed to the process chambers (containing the pre-loaded primers and probes), the temperature of the materials in each of the process chambers can be raised to a selected base temperature (e.g., 60°C) to begin the PCR amplification. As the device rotates, a laser or other electromagnetic energy source can be used to raise the temperature of the sample materials in each of the process chambers to an upper target temperature at which, e.g., denaturing of the DNA occurs.

After reaching the target temperature, the sample materials are brought back down to the base temperature. In the methods of the present invention, the base temperature can be reached through convective cooling as the device rotates. That convective cooling alone, or in connection with conductive cooling using a base plate, impinging fluid jets, etc., preferably provides for rapid cooling of the sample materials, followed by rapid heating back up to the target temperature. The rapid heating and cooling is advantageous in that a desired number of thermal cycles can be completed in a relatively short period of time.

Device of the present invention with process chamber arrays such as those illustrated in, e.g., Figures 13-16, may be used to provide integrated processing of starting sample materials by, e.g., amplification of a starting sample material within a process chamber array on a device. Each of the process chamber arrays include a number of

chambers that are preferably arranged generally radially on a device (such that centrifugal forces can move fluids sequentially from chamber to chamber). The chambers within each of the arrays are in fluid communication using channels or other conduits that may, in some embodiments, include valve mechanisms to control the movement as desired.

One example of an integrated process that can be performed in a process chamber array is schematically illustrated in Figure 17 where a loading chamber 762 is provided to receive, e.g., a starting sample material. The array and one illustrative method of using the array will be described below. The illustrative method involves PCR amplification, followed by Sanger sequencing to obtain a desired end product. This combination of processes is, however, intended to be illustrative only and should not be construed as limiting the present invention.

Starting sample material, e.g., lysed blood cells, is provided in the chamber 762. A filter 763 is preferably provided to filter the starting sample material as it moves from the loading chamber 762 to the first process chambers 750a. The filter 763 is, however, optional and may not be required depending on the properties of the starting sample material.

The first process chambers 750a may preferably include suitable PCR primers as supplied, e.g., dried down in each of the chambers 750a. Each of the chambers 750a may include the same primer or different primers depending on the nature of the investigation being performed on the starting sample material. One alternative to providing the primers in the process chambers 750a before loading the sample is to add a suitable primer to the loading chamber 762 with the starting sample material (provided that the primer is capable of passing through the filter 763, if present).

After locating the starting sample material and any required primers in the process chambers 750a, the materials in the process chambers 750a are thermally cycled under conditions suitable for PCR amplification of the selected genetic material.

After completion of the PCR amplification process, the materials in each of the first process chambers 750a may be moved through another filter chamber 752a (one filter chamber 752a for each process chamber 750a) to remove unwanted materials from the amplified materials, e.g., PCR primers, unwanted materials in the starting sample that were not removed by filter 763, etc. The filter chambers 752a may, for example, contain size

exclusion substances, such as permeation gels, beads, etc. (e.g., MicroSpin or Sephadex available from Amersham Pharmacia Biotech AB, Uppsala, Sweden).

After clean-up of the sample materials in the filter chambers 752a, the filtered PCR amplification products from each of the first process chambers 750a are moved into a pair of multiplexed second process chambers 750b for, e.g., Sanger sequencing of the genetic materials amplified in the first process chambers 750a through appropriate control of the thermal conditions encountered in second process chambers 750b.

After the desired processing has been performed in the second process chambers 750b, the processed material (Sanger sequenced sample material if that is the process performed in the process chambers 750b) is moved from each of the process chambers 750b through another set of filter chambers 752b to remove, e.g., dyes or other unwanted materials from the product of the second process chambers 750b. The filtered product is then moved from the filter chambers 752b into output chambers 750c where it can be removed.

As with the process chamber arrays illustrated in Figures 13-16, it is also preferred that process chamber arrays such as the array illustrated in Figure 17 be arranged generally radially on a device such that rotation of the device will move materials from the loading chamber 762 towards the output chambers 750c. More preferably, it is preferred that two or more of the process chamber arrays illustrated in Figure 17 be arranged on a single device, with the loading chambers 762 of each array located closest to the axis or rotation such that the materials can be moved through the array by centrifugal forces developed during rotation. Alternatively, the arrays may be located on a device that is held in a manner that allows rotation of device containing the array such that centrifugal forces move the materials from the loading chamber 762 towards the output chambers 750c.

A variety of advantages of the integrated process chamber array illustrated in Figure 17 stem from the ability to move from a raw starting sample material to an isolated sequenced product in a single device. Among those advantages are reductions in the number physical transfers (by pipetting, etc.) that can be problematic when working with small volumes of materials. Another advantage is that multiple parallel processes can be simultaneously performed, providing potential improvements in confidence levels regarding the accuracy of the process results. In addition, there may be an enhanced level

of control in ensuring that the process chambers see the same conditions with respect to, e.g., thermal cycling, etc.

Figures 18-20 illustrate another embodiment of a device and methods according to the present invention incorporating valves separating the process chambers within each process chamber array. The illustrated device 810 includes a plurality of process chamber arrays in manner similar to that described with respect to the embodiment illustrated in Figures 13-16 above. One of the process chamber arrays is depicted in the enlarged cross-sectional view of Figure 19.

The device 810 includes a first cover layer 830 attached to a first major side 822 of the substrate 820 and a second cover layer 840 attached to a second major side 824 of the substrate 820. The substrate 820 and cover layers 830 and 840 may be attached by any suitable technique or techniques, including, but not limited to, adhesives, welding (chemical and/or thermal), etc.

The first cover layer 830 may be homogeneous or it may include multiple sub-layers as described above. It may be preferred that the first cover layer 830 be reflective for electromagnetic energy of selected wavelengths as described above. The second cover layer 840 may include, e.g., an adhesive on a carrier layer, both of which may be optically clear or otherwise transmissive to electromagnetic energy of selected wavelengths.

Among the features formed in the substrate 820 are a loading chamber 860 that, in the illustrated embodiment, is in the form of an annular ring. Each of the process chamber arrays also include inner or first process chambers 850a and outer or second process chambers 850b located further out radially from a center of the device 810.

The loading chamber 860 is in fluid communication with the inner process chamber 850a through channel 862. As a result, rotation of the device 810 about its center will force sample material to move from the loading chamber 860 into the first process chamber 850a where the first thermal processing of the sample material may be performed.

The device 810 also includes a valve 870 located between and separating the inner and outer process chambers 850a and 850b. The valve 870 is normally closed when the device 810 is supplied to a user to prevent movement of the sample material from the first process chamber 850a into the second process chamber 850b.

The valve 870 may preferably be located within a via 880 that is in fluid communication with inner process chamber 850a through channel 882 on one side and in fluid communication with the outer process chamber 850b through channel 884 on the opposite side. It may be preferred that the via 880 be formed such that it extend between the first and second major surfaces 822 and 824 of the substrate 820 as depicted.

The valve 870 includes an impermeable disc 872 that prevents fluids from moving between the process chambers 850a and 850b when it is intact. The impermeable disc 872 is preferably distinct from the substrate 820, i.e., it is preferably made of a material that is different than the material used for the substrate 820. By using different materials for the substrate 820 and the impermeable disc 872, each material can be selected for its desired characteristics.

The impermeable disc 872 may be made of any suitable material, although it may be preferred that the material of the disc 872 form voids without the production of any significant byproducts, waste, etc. that could interfere with the reactions or processes taking place in process chambers. A preferred class of materials are pigmented oriented polymeric films, such as, for example, films used to manufacture commercially available can liners or bags. A suitable film may be a black can liner, 1.18 mils thick, available from Himolene Incorporated, of Danbury, Connecticut under the designation 406230E.

It may further be preferred that the impermeable disc 872 of the valve 870 include material susceptible of absorbing electromagnetic energy of selected wavelengths and converting that energy to heat, resulting in the formation of a void in the impermeable disc 872. The absorptive material may be contained within the impermeable disc 872 or coated on a surface thereof.

The valve 870 illustrated in Figure 19 also includes an optional permeable support 874 located proximate at least one side of the impermeable disc 872. The support 874 is permeable to the fluids moving between the process chambers 850a and 850b, although it may perform some filtering functions in addition to supporting the impermeable disc 872. It may be preferred that the support 874 be somewhat resilient to assist in sealing the valve 870 by forcing the impermeable disc 872 against the surfaces in the via 880 with sufficient force to prevent fluid passage in ordinary use of the device 810.

It may be preferred that the support 874 be provided in the form of a porous disc as illustrated in Figure 19. The porous disc support 874 may preferably be coextensive with the impermeable disc 872 used in the valve 870. Alternative forms of the support may include rings, sleeves, or any other structure or material that can support at least a portion of the impermeable disc 872 in the valve 870.

In some embodiments, it may be desirable that the porous disc support 874 reflect electromagnetic energy of selected wavelengths to assist in the opening of the valve 870 and/or prevent the electromagnetic energy from reaching any underlying fluids, sample materials, etc.

It may be preferred that the porous disc support 874 be hydrophobic to reduce or prevent fluid contact with the impermeable disc 872. Alternatively, it may be preferred that the porous disc support 874 be hydrophilic to promote fluid contact with the impermeable disc 872 of the valve 870.

Examples of suitable materials for a porous disc support may include, but are not limited to, porous plugs or membranes, including scintered polypropylene and scintered polyethylene plugs or membranes, e.g., such as those commercially available from Porex Corporation, Fairburn, Georgia.

The valve 870 is opened by forming a void in the impermeable disc 872. The void may be formed by electromagnetic energy of any suitable wavelength. It may be preferred that laser energy of a suitable wavelength be used. A potential advantage of using laser energy is that the same laser used to heat the materials in the process chambers may be used to form the voids needed to place the process chambers in fluid communication with each other.

It may further be desirable to place the impermeable disc 872 of the valve 870 within a via 880 as illustrated in Figure 19. Locating the impermeable disc 872 within a via 880 and directing electromagnetic energy of some wavelengths into the via 880 may result in some advantages in that the walls of the via 880 may reflect and/or focus at least some of the energy to assist in formation of the void in the disc 872.

The device 810 includes an optional control pattern depicted in Figure 20 that includes indicators 890a, 890b, 892, and 894 useful in controlling the electromagnetic energy delivered to the process chambers and/or valves. In the illustrated embodiment, the

control pattern is located on the first cover layer 830, although other suitable locations may alternatively be used.

The indicators used in the control pattern have at least one characteristic indicative of the electromagnetic energy to be delivered to the associated process chamber and/or valve. The characteristics may include size, shape, color, or any other distinguishing feature that may be detected and used to control the delivery of electromagnetic energy. In the illustrated embodiment, the primary distinguishing characteristics include size and/or shape. It may be preferred that the indicators be detected optically (based on, e.g., contrast with the surrounding surface of the device 810, sensing of a void formed through the device 810, etc.).

The illustrated control pattern includes a first set of indicators 890a associated with some of the inner process chambers 850a and a second set of indicators 890b associated with the rest of the inner process chambers 850a. The difference between the sets of indicators is their size, with the indicators 890a being smaller than the indicators 890b. That size may be used to control the amount of energy delivered to the process chambers associated with each indicator, e.g., the larger indicators 890b may result in the delivery of more energy to their associated process chambers 850a. Alternatively, the differently sized indicators 890a and 890b may be used to control the wavelength of the electromagnetic energy delivered to the associated process chambers 850a (with each of the different indicators denoting a different wavelength of energy). In yet another alternative, both the amount and wavelength of the energy delivered to each process chamber may vary depending on the characteristics of the associated indicators.

One potentially desirable method for using indicators 890a and 890b based on their sizes and the rotation of the device 810 is to begin delivery of electromagnetic energy when the leading edge of the relevant indicator passes a detector and ceasing delivery of that energy when the trailing edge of the same indicator passes the detector. The electromagnetic energy may be controlled at its source by cycling or the delivery may be interrupted by, e.g., a shutter, rotating mirror, or other system.

The indicators 890a and 890b are each associated with only one of the process chambers 850a. Indicator 892, however, is associated with all of the valves 870 on the device 810 and can be used to control the delivery of electromagnetic energy needed to

open the valves 870 as described above. In a similar manner, delivery of electromagnetic energy to multiple process chambers 850a could be effected with one indicator in some systems.

Indicators 894 are associated with the outer process chambers 850b and can be used to control delivery of electromagnetic energy to those process chambers. As illustrated, the shape of the indicators 894 is different from the other indicators and those different characteristics may be used for control purposes.

Although the indicators in the illustrated control pattern are located generally in registration with the process chamber or valve with which they are associated, the control pattern need not be so provided. For example, the control pattern may occupy only a portion of the surface of the device 810, e.g., an outer annular ring.

In another alternative, the control pattern or portions thereof may be used to control other components of a system using the device 810. For example, indicators may be provided that control the type of detectors used to monitor the process chambers for, e.g., a desired product, temperature, pH, etc. Such indicators may be provided in the form of bar codes.

Figures 21 and 22 illustrate another construction of a device 910. The device is similar in many respects the device 810. One difference, however, is that the substrate 920 includes an upper layer 920a and a lower layer 920b with a valve layer 976 located between the upper layer 920a and lower layer 920b. The valve layer 976 forms the impermeable discs 972a and 972b of the valves 970a and 970b. Unlike the impermeable discs 872 of the valves 870 of the device 810 (which are separate and distinct from each other), the impermeable discs 972a and 972b are formed of portions of the same valve layer 976 which extends between the different valves 970a and 970b.

The layers 920a, 920b and valve layer 976 may be attached together by any suitable technique or combination of techniques. For example, they may be adhesively attached, welded (thermally, chemically, etc.), heat-sealed, etc. It may be desirable that the valve layer 976 be used to form the impermeable discs of all of the valves on the device 910 or only some of the valves. If the valve layer 976 is used to form the impermeable discs of all of the valves, it may be desirable that the valve layer 976 be coextensive with the major surfaces of the device 910. The laminated construction of the device 910 may provide

advantages in the manufacturing of the devices 910 by allowing the sue f web or other continuous manufacturing processes.

The valves 970a and 970b are used to separate the process chambers 950a, 950b and 950c and control movement of the sample material 958 between the chambers. As illustrated in Figure 21, the sample material 958 is located in process chamber 950a which is not in fluid communication with process chamber 950b due to the closed state of the valve 970a.

In Figure 22, however, the impermeable disc 972a of valve 970a includes a void 973 formed therein after delivery of the appropriate electromagnetic energy 975 into the via 980 containing the valve 970. That void allow the sample material 958 to move into the process chamber 950b from process chamber 950a. In the illustrated embodiment, process chamber 950b includes filter material 959 through which the sample material 958 passes on its way to process chamber 950c.

Patents, patent applications, and publications disclosed herein are hereby incorporated by reference as if individually incorporated. It is to be understood that the above description is intended to be illustrative, and not restrictive. Various modifications and alterations of this invention will become apparent to those skilled in the art from the foregoing description without departing from the scope of this invention, and it should be understood that this invention is not to be unduly limited to the illustrative embodiments set forth herein.

**What is claimed is:**

1. A method of conducting a thermal cycling process comprising:

providing a device comprising a plurality of process chambers, each of the process chambers defining a volume for containing sample material;

providing sample material in at least some of the process chambers;

delivering electromagnetic energy to the process chambers to raise the temperature of the sample material in the process chambers; and

rotating the device about an axis of rotation while delivering the electromagnetic energy, wherein the temperature of the sample material in the process chambers is controlled as the substrate rotates.

2. The method of claim 1, further comprising monitoring the temperature of the sample material in the process chambers while rotating the device.

3. The method of claim 1, further comprising monitoring the temperature of the sample material in the process chambers while rotating the device, wherein the delivery of electromagnetic energy is controlled to cycle the temperature of the sample material in the process chambers between a selected upper temperature and a selected lower temperature.

4. The method of claim 1, further comprising disrupting airflow over the device while rotating the device.

5. The method of claim 4, wherein the disrupting comprises providing at least one baffle on an exterior surface of the device.

6. The method of claim 4, wherein the disrupting comprises directing a fluid at the device while rotating the device.

7. The method of claim 1, further comprising detecting electromagnetic energy emitted from the sample material in the process chambers while rotating the device.

8. The method of claim 1, wherein the device comprises at least one valve separating at least one selected pair of the plurality of process chambers, the valve comprising an impermeable disc, the method further comprising placing the selected pair of process chambers in fluid communication by forming a void in the impermeable disc of the valve.

9. The method of claim 1, wherein the device comprises a plurality of valves, each of the valves separating selected pairs of the plurality of process chambers with an impermeable disc, the method further comprising placing the selected pairs of process chambers in fluid communication by forming a void in each impermeable disc, and further wherein the impermeable discs of a plurality of the valves comprise a portion of a valve layer.

10. The method of claim 8, wherein the at least one valve further comprises a permeable support proximate the impermeable disc.

11. The method of claim 10, wherein the impermeable disc and permeable support are located within a via extending between opposing major surfaces of a substrate of the device.

12. The method of claim 11, wherein forming the void in the impermeable disc comprises directing electromagnetic energy into the via.

13. The method of claim 1, wherein the device further comprises a control pattern, the control pattern comprising at least one indicator associated with each of the plurality of process chambers, the method further comprising:

detecting at least one characteristic of the at least one indicator; and

controlling the electromagnetic energy delivered to each process chamber associated with that indicator based on the detection of the at least one characteristic.

14. The method of claim 13, further comprising controlling the electromagnetic energy delivered to a plurality of the plurality of process chambers based on detecting the at least one characteristic of only one of the indicators.

15. The method of claim 13, wherein each indicator is associated with only one of the plurality of process chambers.

16. The method of claim 13, wherein the detecting is based on optical contrast of the indicators with a surrounding surface.

17. The method of claim 13, wherein controlling the electromagnetic energy comprises controlling the amount of the electromagnetic energy to be delivered.

18. The method of claim 13, wherein controlling the electromagnetic energy comprises controlling the wavelength of the electromagnetic energy to be delivered.

19. A method of processing sample material comprising:

providing a device comprising a plurality of process chamber arrays, each of the process chamber arrays comprising a loading chamber, a first process chamber, and a second process chamber;

providing sample material in the loading chamber of at least one of the process chamber arrays;

moving the sample material from the loading chamber into the first process chamber by rotating the device;

controlling the temperature of the sample material in the first process chamber by rotating the device about an axis of rotation while delivering electromagnetic energy to the first process chamber;

moving the sample material from the first process chamber to the second process chamber by rotating the device; and

controlling the temperature of the sample material in the second process chamber by rotating the device about an axis of rotation while delivering electromagnetic energy to the second process chamber.

20. The method of claim 19, further comprising filtering the sample material while moving the sample material from the first process chamber to the second process chamber.

21. The method of claim 19, wherein the sequential process chambers further comprise an output chamber in fluid communication with the second process chamber, and wherein the method further comprises moving the sample material from the second process chamber to the output chamber by rotating the device.

22. The method of claim 21, further comprising filtering the sample material while moving the sample material from the second process chamber to the output chamber.

23. The method of claim 19, wherein controlling the temperature of the sample material in the first process chamber comprises performing PCR using the sample material.

24. The method of claim 23, wherein controlling the temperature of the sample material in the second process chamber comprises Sanger sequencing the sample material in the second process chamber.

25. The method of claim 19, wherein the device comprises at least one valve separating the first and second process chambers in each of the process chamber arrays, the valve comprising an impermeable disc, the method further comprising placing the first and second process chambers in fluid communication by forming a void in the impermeable disc of the at least one valve.

26. The method of claim 19, wherein the at least one valve further comprises a permeable support proximate the impermeable disc.

27. The method of claim 26, wherein the impermeable disc and permeable support are located within a via extending between opposing major surfaces of a substrate of the device.

28. The method of claim 27, wherein forming the void in the impermeable disc comprises directing electromagnetic energy into the via.

29. The method of claim 19, wherein the device further comprises a control pattern, the control pattern comprising at least one indicator associated with each of the process chambers, the method further comprising:

detecting at least one characteristic of the at least one indicator; and

controlling the electromagnetic energy delivered to each process chamber associated with that indicator based on the detection of the at least one characteristic.

30. The method of claim 29, further comprising controlling the electromagnetic energy delivered to a plurality of the process chambers based on detecting the at least one characteristic of only one of the indicators.

31. The method of claim 29, wherein each indicator is associated with only one of the plurality of process chambers.

32. The method of claim 29, wherein the detecting is based on optical contrast of the indicators with a surrounding surface.

33. The method of claim 29, wherein controlling the electromagnetic energy comprises controlling the amount of the electromagnetic energy to be delivered.

34. The method of claim 29, wherein controlling the electromagnetic energy comprises controlling the wavelength of the electromagnetic energy to be delivered.

35. A device for use in thermal processing, the device comprising:

a substrate comprising first and second major surfaces;

a plurality of process chambers in the device, each of the process chambers defining a volume for containing a sample; and

a plurality of valves with at least one of the valves located between selected pairs of the process chambers, each valve comprising an impermeable disc distinct from the substrate, wherein the impermeable disc of each of the valves separates the selected pairs of process chambers.

36. The device of claim 35, wherein the substrate comprises a valve layer, and further wherein the impermeable discs of a plurality of the valves each comprise a portion of the valve layer.

37. The device of claim 36, wherein the impermeable discs of all of the valves comprise a portion of the valve layer.

38. The device of claim 37, wherein the valve layer is coextensive with the first and second major surfaces of the substrate.

39. The device of claim 35, wherein the impermeable disc of each valve is separate and distinct from the impermeable discs of the other valves.

40. The device of claim 35, wherein each of the valves comprises a permeable support proximate the impermeable disc.

41. The device of claim 40, wherein the permeable support comprises a ring comprising an opening formed therein, wherein the portion of the impermeable disc proximate the opening is unsupported.

42. The device of claim 40, wherein the permeable support comprises a porous disc coextensive with the impermeable disc.

43. The device of claim 42, wherein the porous disc reflects electromagnetic energy of selected wavelengths.

44. The device of claim 35, wherein at least some of the plurality of valves are located within vias extending between the first and second major surfaces of the substrate

45. The device of claim 35, further comprising a reflective layer that is substantially continuous over the first major surface, and further wherein the reflective layer reflects electromagnetic energy of selected wavelengths.

46. The device of claim 45, wherein the reflective layer comprises a metallic layer.

47. The device of claim 35, wherein the selected pairs of the process chambers are arranged radially from a center of the device with each pair comprising an inner process chamber and an outer process chamber, and further wherein a void formed in the impermeable disc of one of the valves places one of the selected pairs of process chambers in fluid communication with each other, whereby rotation of the device can move sample material between the selected pairs of process chambers.

48. The device of claim 47, wherein a plurality of inner process chambers are in fluid communication with a loading chamber.

49. The device of claim 35, further comprising a control pattern on the device, the control pattern comprising at least one indicator associated with each of the plurality of process chambers, each of the indicators having at least one characteristic indicative of electromagnetic energy to be delivered to each process chamber associated with that indicator, whereby the delivery of the electromagnetic energy to selected process chambers can be controlled.

50. The device of claim 35, further comprising a control pattern on the device, the control pattern comprising at least one indicator associated with each of the plurality of valves, each of the indicators having at least one characteristic indicative of electromagnetic energy to be delivered to each valve associated with that indicator, whereby the delivery of the electromagnetic energy to the valves can be controlled.

51. The device of claim 50, wherein each indicator is associated with a plurality of the plurality of valves.

52. The device of claim 50, wherein each indicator is associated with only one of the plurality of process chambers.

53. The device of claim 50, wherein one of the at least one characteristic of the indicators is indicative of the amount of the electromagnetic energy to be delivered.

54. The device of claim 50, wherein one of the at least one characteristic of the indicators is indicative of the wavelength of the electromagnetic energy to be delivered.

55. A device for use in thermal processing, the device comprising:

a substrate comprising first and second major surfaces;

a plurality of process chambers in the device, each of the process chambers defining a volume for containing a sample; and

a control pattern on the device, the control pattern comprising at least one indicator associated with each of the plurality of process chambers, each of the indicators having at least one characteristic indicative of electromagnetic energy to be delivered to each process chamber associated with that indicator, whereby the delivery of the electromagnetic energy to selected process chambers can be controlled.

56. The device of claim 55, wherein each indicator is associated with a plurality of the plurality of process chambers.

57. The device of claim 55, wherein each indicator is associated with only one of the plurality of process chambers.

58. The device of claim 55, wherein the indicators are defined by optical contrast with a surrounding surface.

59. The device of claim 55, wherein one of the at least one characteristic of the indicators is indicative of the amount of the electromagnetic energy to be delivered.

60. The device of claim 55, wherein one of the at least one characteristic of the indicators is indicative of the wavelength of the electromagnetic energy to be delivered.

61. A device for use in thermal processing, the device comprising:

a substrate comprising first and second major surfaces;

a plurality of process chambers in the device, each of the process chambers defining a volume for containing a sample; and

a baffle structure on the first major surface of the substrate, wherein airflow over the first major surface is disrupted when the substrate is rotated.

62. The device of claim 61, further comprising a cover layer attached to the first major surface of the substrate, wherein at least a portion of each of the process chambers comprises a structure formed in the cover layer, and further wherein the process chamber structure forms at least a portion of the baffle structure.

63. The device of claim 61, further comprising a distribution system in fluid communication with the plurality of process chambers, wherein the distribution system comprises a plurality of distribution channels at least partially formed in a cover layer attached to the first major surface of the substrate.

64. The device of claim 63, wherein each of the distribution channels forms at least a portion of the baffle structure.

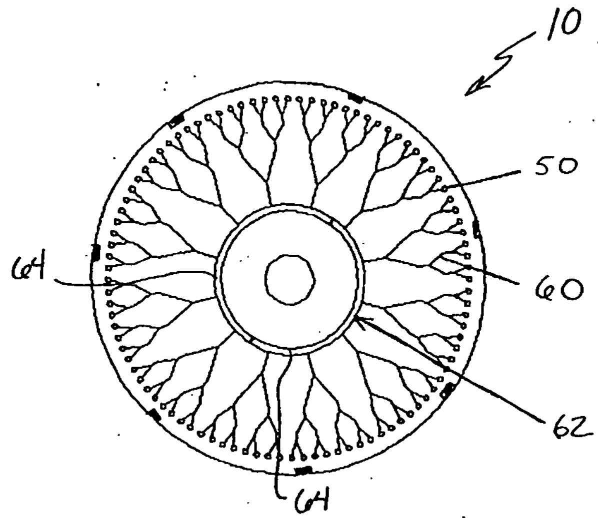



FIG. 1

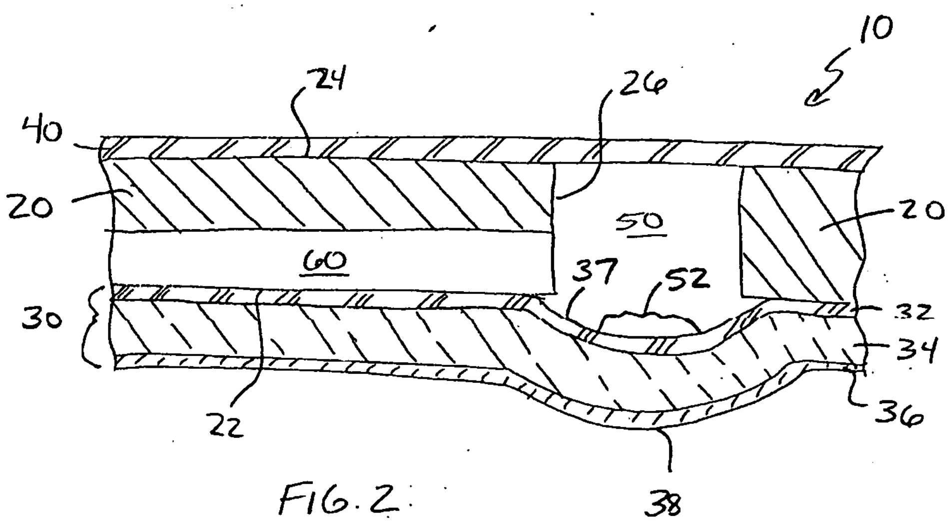



FIG. 2

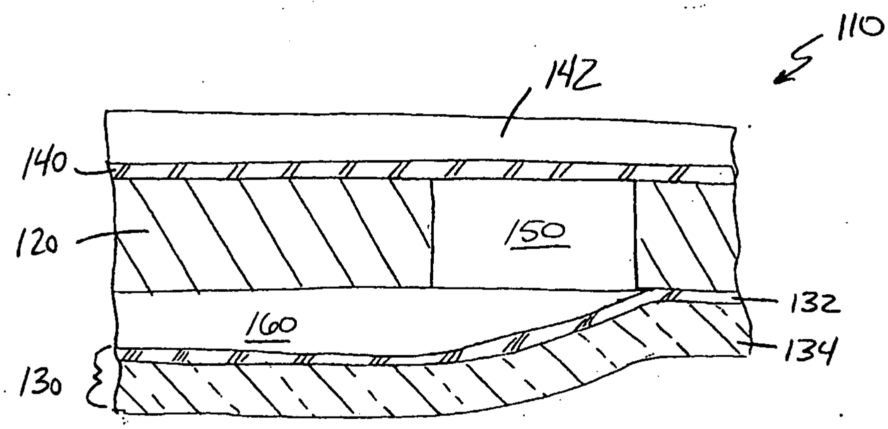



FIG. 3

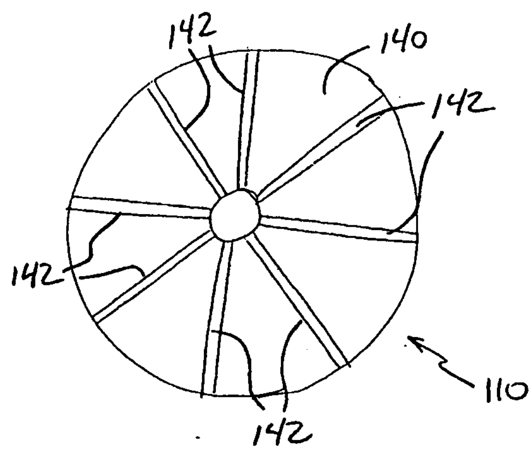



FIG. 4

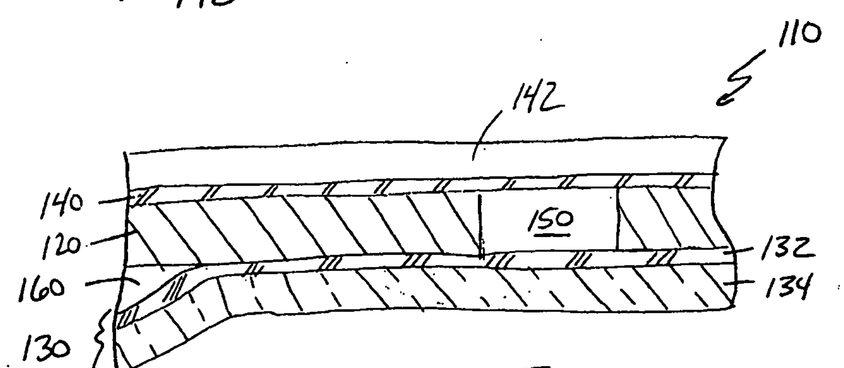



FIG. 5

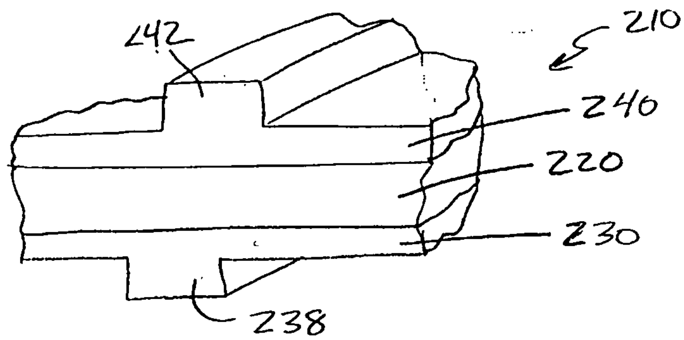



FIG. 6

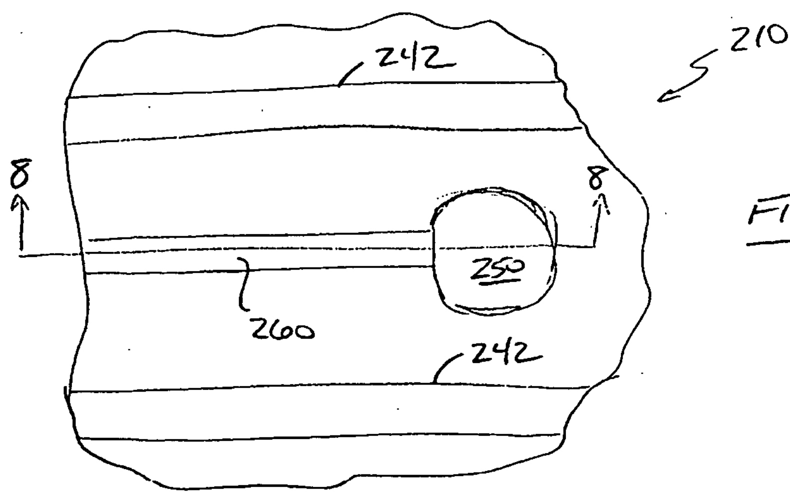



FIG. 7

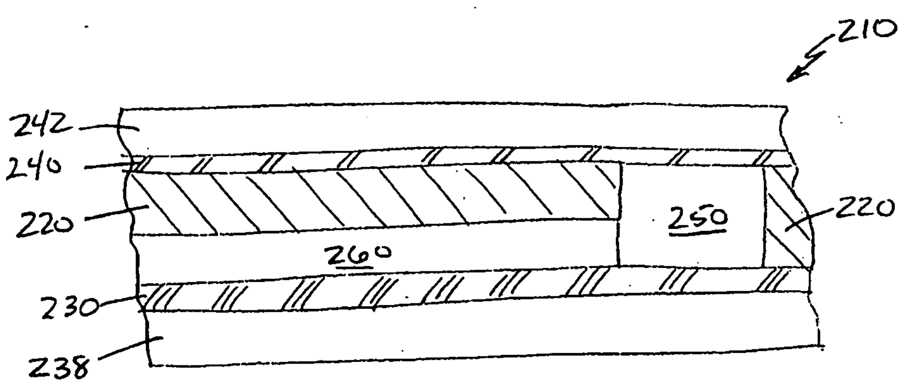



FIG. 8

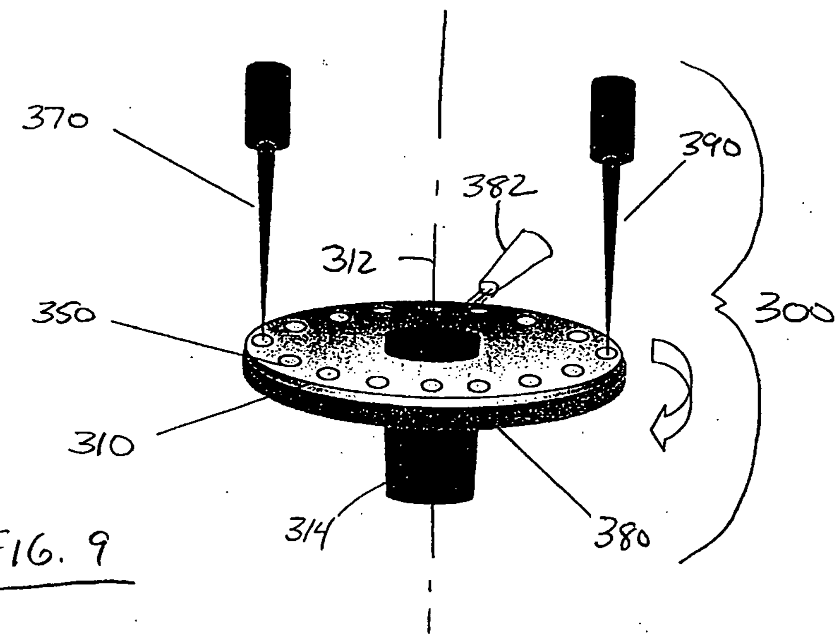



FIG. 9

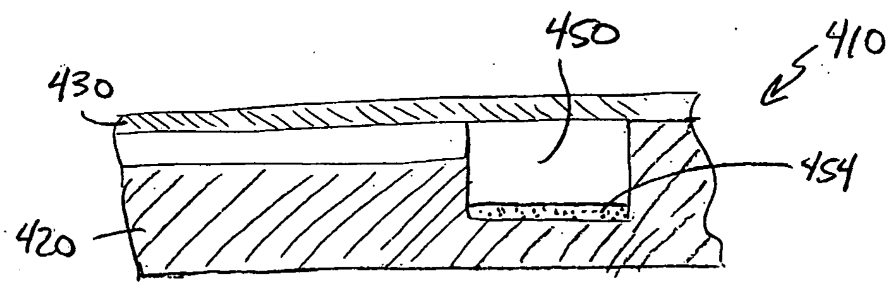



FIG. 10

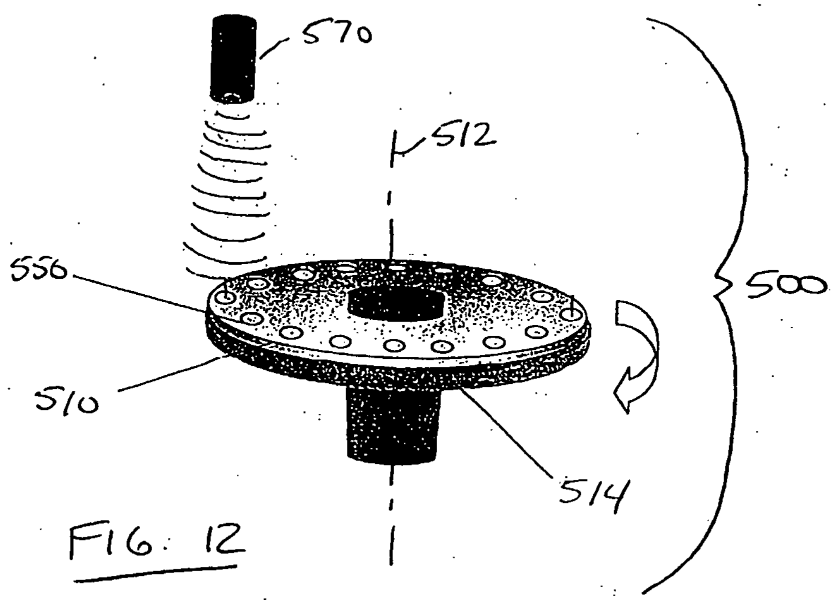



FIG. 12

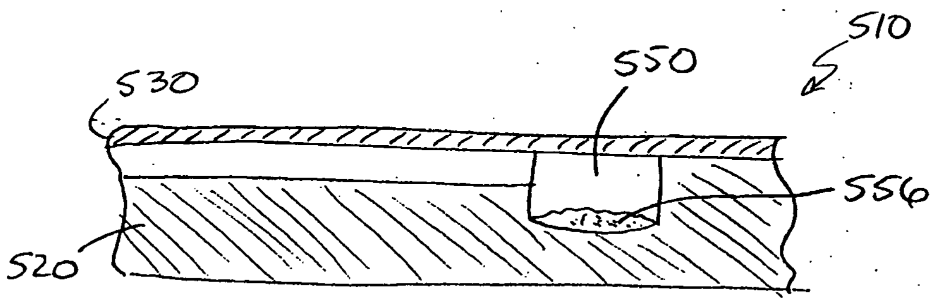



FIG. 11

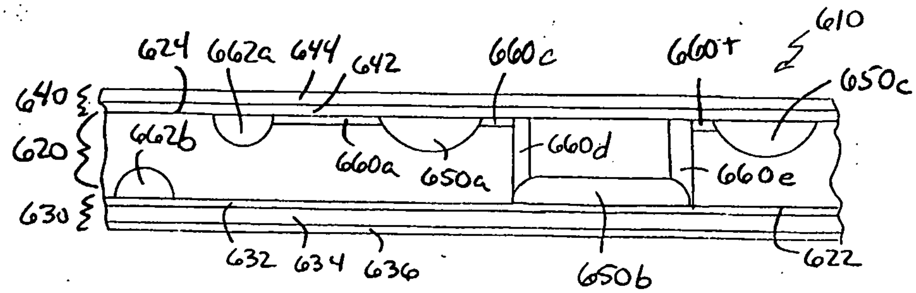



FIG. 13

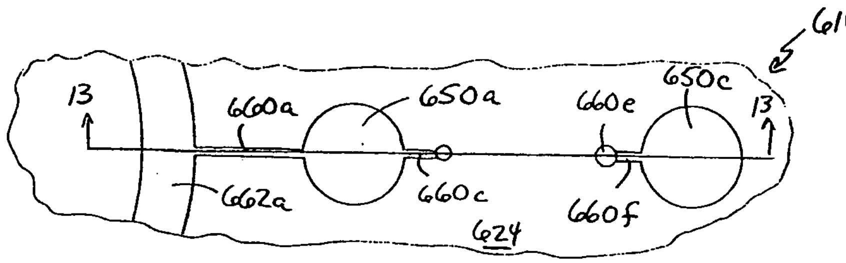



FIG. 14

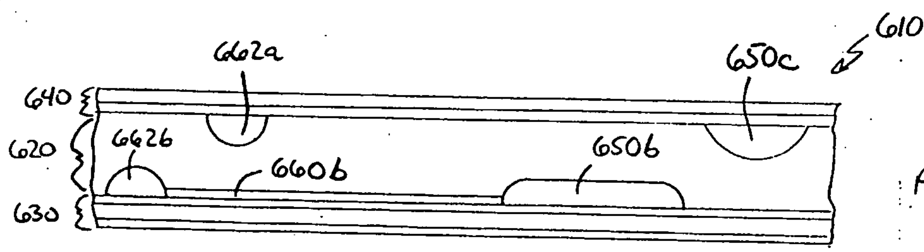



FIG. 15

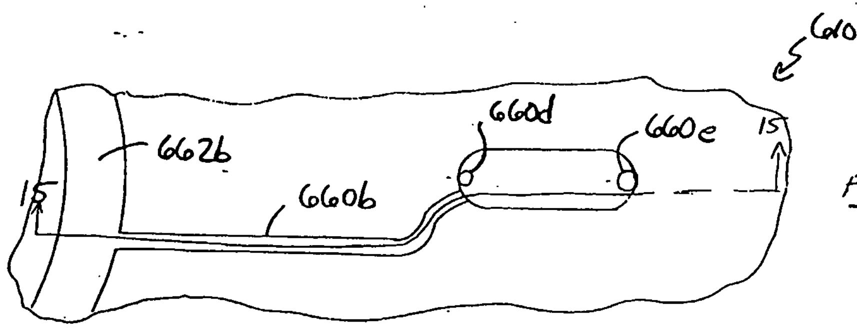



FIG. 16

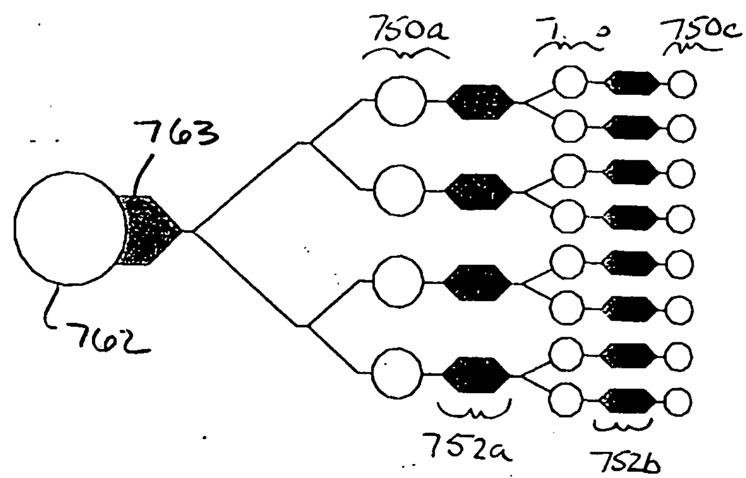



FIG. 17

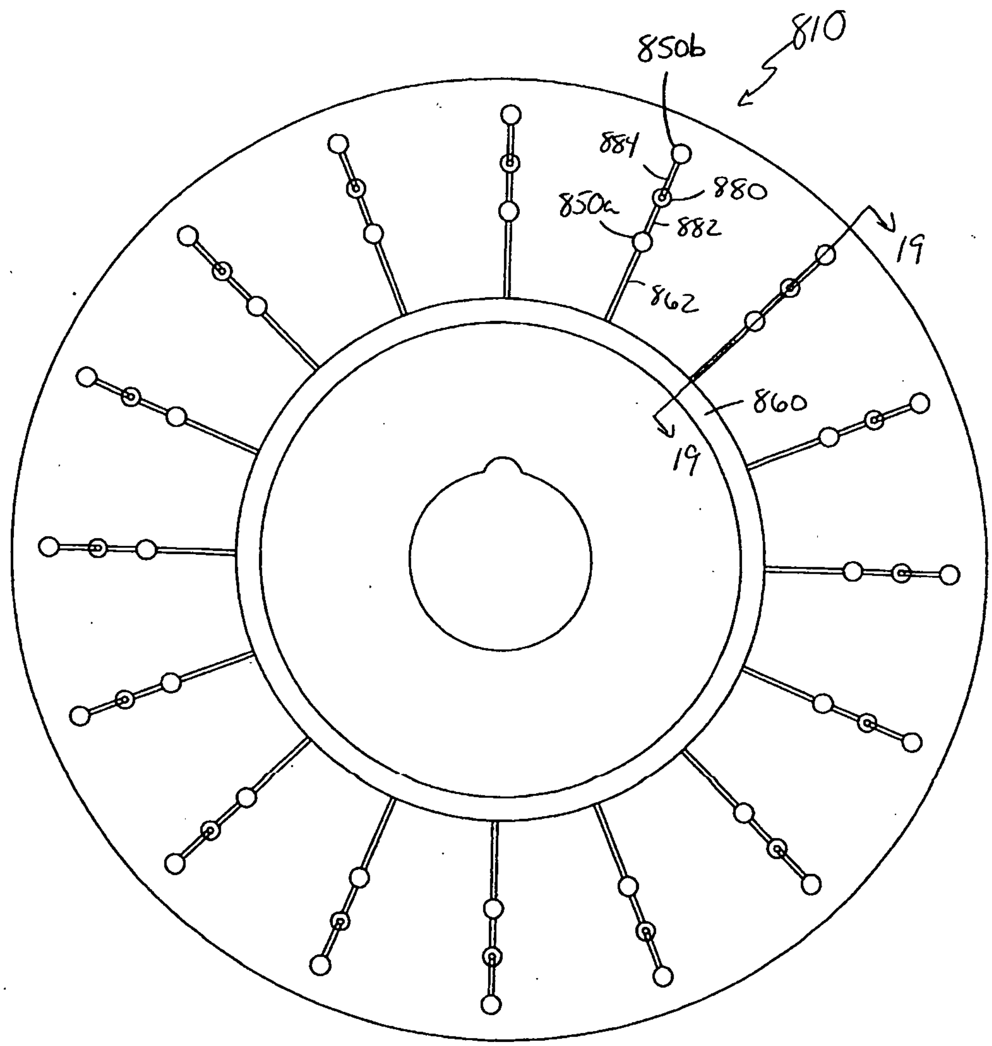
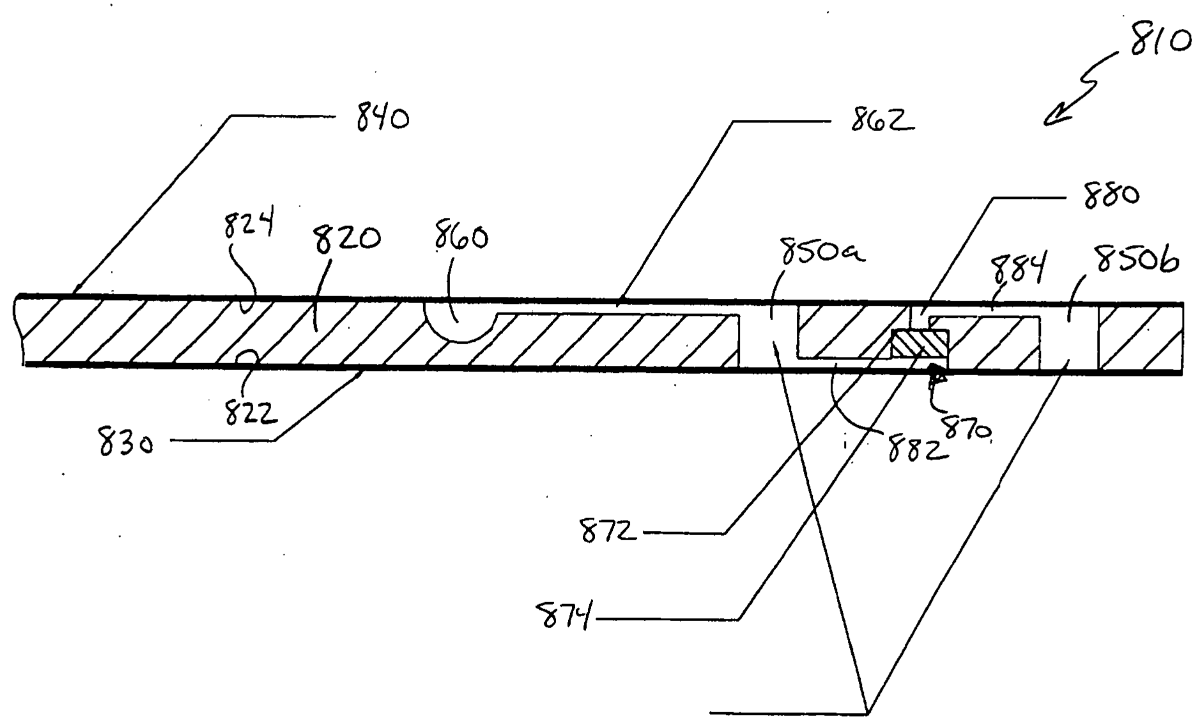



FIG. 18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874

FIG. 19

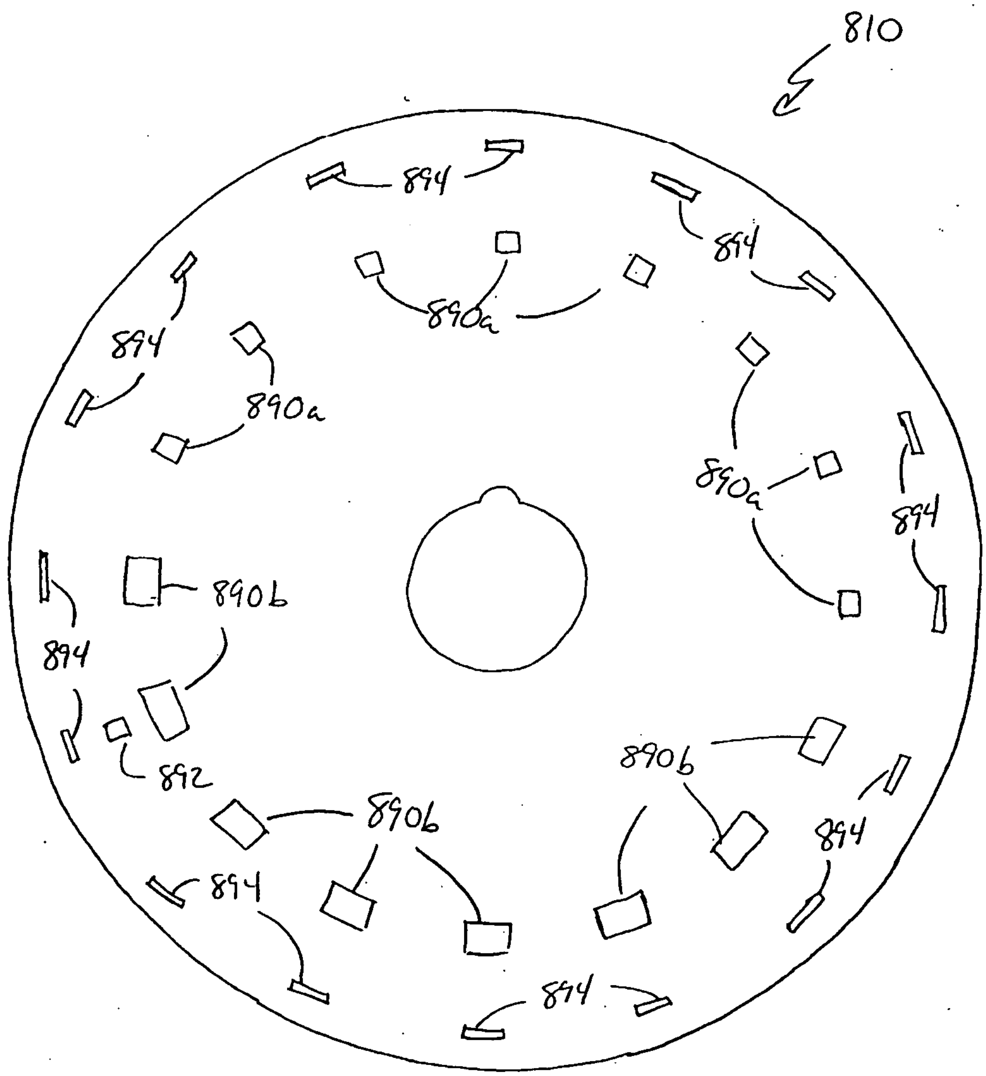
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FIG 20

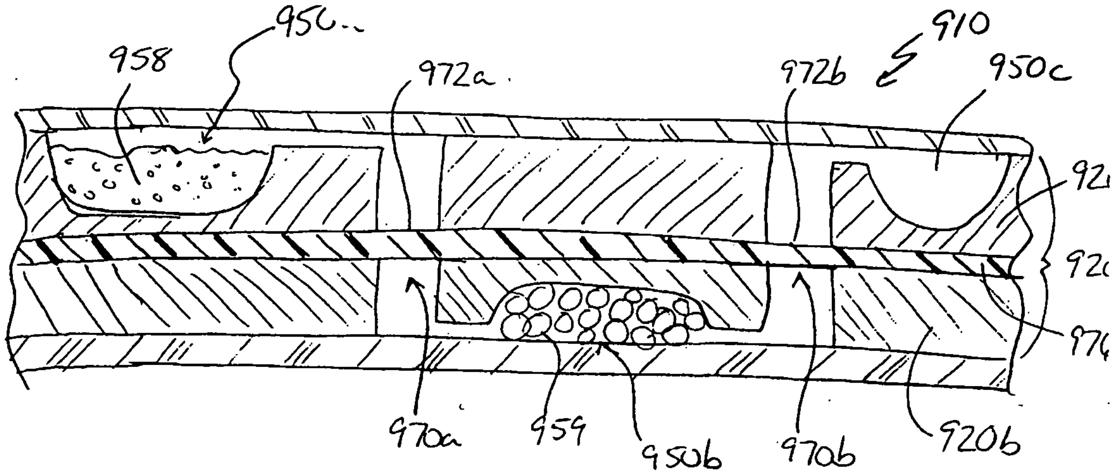
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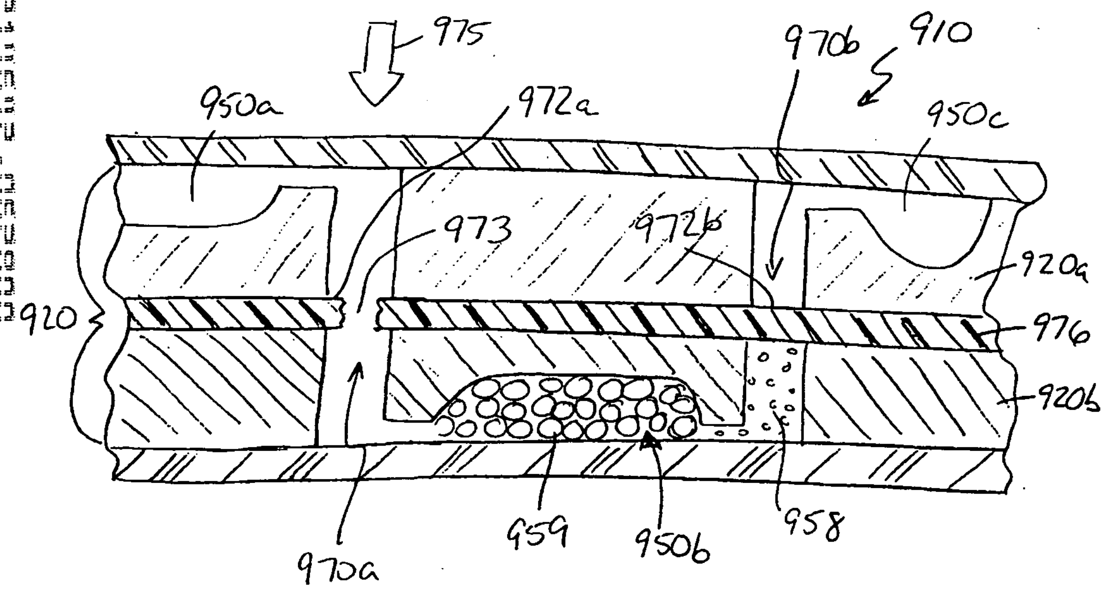
FIG. 21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950b
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970a

FIG. 22

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**Exhibit A**

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| APPLICATION NUMBER | FILING DATE | GRP ART UNIT | FIL FEE REC'D | ATTY.DOCKET.NO | DRAWINGS | TOT CLAIMS | IND CLAIMS |
|---|---|---|---|---|---|---|---|
| 09/710,184 | 11/10/2000 | 1743 | 0 | 55265-USA-9A.002 | 11 | 30 | 3 |

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? ?, Residence Not Provided;

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**Foreign Applications**

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**Title**

Centrifugal filling of sample processing devices

**Preliminary Class**

204

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**Data entry by :** LADRINGAN, JUDITH **Team :** OIPE **Date:** 03/12/2001

OIPE JC136 FEB 19 2004 PATENT & TRADEMARK OFFICE

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# CENTRIFUGAL FILLING OF SAMPLE PROCESSING DEVICES

## Field of the Invention

The present invention relates to the field of sample processing devices. More particularly, the present invention relates to sample processing devices and methods of distributing sample material in sample processing devices.

## Background

Many different chemical, biochemical, and other reactions are performed on a variety of sample materials. Although it may be possible to process samples individually and obtain accurate sample-to-sample results, individual processing of samples can be time-consuming and expensive.

One approach to reducing the time and cost of processing multiple samples is to use a device including multiple chambers in which different portions of one sample or different samples can be processed simultaneously. This approach, however, presents several issues related to distribution of sample materials to the multiple chambers in the devices. Other problems may be encountered in the migration of materials between chambers during processing, which may lead to erroneous test results due to cross-chamber contamination.

## Summary of the Invention

The present invention provides methods and devices for distributing sample material to a plurality of process chambers in a sample processing device by rotating the device about an axis of rotation. The process chambers are located along conduits extending from a loading chamber and, together, the loading chamber, conduits, and process chambers form process arrays that are aligned along a length of the sample processing devices. The process arrays are unvented, i.e., access to the interior volume of the process arrays is available only through the loading chamber.

In other aspects, the present invention may provide sample processing devices including conduits that can be sealed by deforming one or both sides of the sample processing device to restrict or completely close off the conduit. It may be advantageous if the sample processing device includes a pressure sensitive adhesive located between two major sides of the device to assist in sealing of the conduit during and after deformation.

Other aspects of the sample processing devices may include, for example, elongated processing chambers, feeder conduits leading to the process chambers that form feeder conduit angles with the main conduit of less than 90 degrees, etc.

The process arrays in sample processing devices of the present invention may be capable of customization by selective opening and/or closing of fluid paths in the process arrays.

In some methods of centrifugal loading, it may be desirable to compress the sample processing devices during rotation to significantly reduce or eliminate leakage from the conduits and/or process chambers as a result of the centrifugal forces. Compression may be particularly helpful when used in connection with centrifugal loading of sample processing devices constructed using pressure sensitive adhesives.

The present invention also includes, in some aspects, an assembly of a carrier and a sample processing device attached to the carrier. The carrier may integral with the sample processing device, i.e., it may be provided as a single use article, or the carrier may be reusable. The carriers may advantageously include rails to support the main conduits of process arrays on the sample processing device, openings to allow for monitoring of process chambers on the sample processing devices, and other features.

In one aspect, the present invention provides a method of distributing sample material in a sample processing device by providing a sample processing device with first and second opposing ends and at least one unvented process array including a loading chamber located proximate the first end, a main conduit extending towards the second end, and a plurality of process chambers

distributed along the main conduit, wherein the main conduit is in fluid communication with the loading chamber and the plurality of process chambers. The method further includes loading sample material in the loading chamber of each of the process arrays, and transporting the sample material to at least some of the process chambers by rotating the sample processing device about an axis of rotation located proximate the first end of the sample processing device, wherein the process chambers are located further from the axis of rotation than the loading chambers.

In another aspect, the present invention provides a sample processing assembly including a sample processing device with first and second opposing ends and at least one unvented process array comprising a loading chamber located proximate the first end, a main conduit extending towards the second end, and a plurality of process chambers distributed along the main conduit, wherein the main conduit is in fluid communication with the loading chamber and the plurality of process chambers; and a carrier attached to a first major side of the sample processing device, the carrier including a carrier body spaced from at least a portion of the first major side of the sample processing device.

In another aspect, the present invention provides a sample processing device including first and second opposing ends; a plurality of unvented process arrays, each of the process arrays including a loading chamber located proximate the first end; a main conduit extending towards the second end; and a plurality of process chambers distributed along the main conduit, wherein the main conduit is in fluid communication with the loading chamber and the plurality of process chambers; and wherein each of the process chambers is in fluid communication with one of the main conduits through a feeder conduit, and wherein the feeder conduits form feeder conduit angles with the main conduits that are less than 90°.

These and other features and advantages of the present invention are described below in connection with various illustrative embodiments of the devices and methods of the present invention.

Brief Description of the Drawings

Figure 1 is a plan view of one sample processing device.

Figure 2 is an enlarged partial cross-sectional view of one process array on a sample processing device.

Figure 3 is an enlarged partial cross-sectional view of the process array of Figure 2 depicting one method of sealing the main conduit.

Figure 4 is a plan view of one centrifuge system for rotating sample processing devices.

Figure 5 is a plan view of a portion of an alternative process array.

Figure 6 is a cross-sectional view taken along line 6-6 in Figure 5.

Figure 7 is a cross-sectional view taken along line 7-7 in Figure 6.

Figure 8 depicts an alternative set of process arrays for a sample processing device.

Figure 9 depicts an alternative set of process arrays for a sample processing device.

Figure 10 is a perspective view of a sample processing device in which the loading chambers are being separated from the remainder of the sample processing device.

Figure 11 is a perspective view of the sample processing device of Figure 10 after sealing.

Figure 12 is a plan view of another sample processing device.

Figure 13 is a side view of the sample processing device of Figure 12 after folding the device along a line separating the loading chambers from the process chambers.

Figure 14 depicts a sample processing device located within a compression device.

Figure 15 is a plan view of an alternative compression device.

Figure 16 is a cross-sectional view taken along line 16-16 in Figure 15.

Figure 17 is an exploded perspective view of an assembly including a sample processing device and a carrier.

Figure 18 is a perspective view of the carrier of Figure 18 taken from the side of the carrier facing the sample processing device.

Figure 19 is a partial cross-sectional view of a sample processing device and carrier including an optical element.

## Detailed Description of Illustrative Embodiments of the Invention

The present invention provides a sample processing device that can be used in the processing of liquid sample materials (or sample materials entrained in a liquid) in multiple process chambers to obtain desired reactions, e.g., PCR amplification, ligase chain reaction (LCR), self-sustaining sequence replication, enzyme kinetic studies, homogeneous ligand binding assays, and other chemical, biochemical, or other reactions that may, e.g., require precise and/or rapid thermal variations. More particularly, the present invention provides sample processing devices in which sample material is delivered to the process chambers by rotating the devices. The methods may also include sealing of the sample processing devices after sample material distribution.

Although various constructions of illustrative embodiments are described below, sample processing devices of the present invention may be manufactured according to the principles described in U.S. Provisional Patent Application Serial No. 60/214,508 filed on June 28, 2000 and titled THERMAL PROCESSING DEVICES AND METHODS (Attorney Docket No. 55265USA19.003); U.S. Provisional Patent Application Serial No. 60/214,642 filed on June 28, 2000 and titled SAMPLE PROCESSING DEVICES, SYSTEMS AND METHODS (Attorney Docket No. 55266USA99.003); U.S. Provisional Patent Application Serial No. 60/237,072 filed on October 2, 2000 and titled SAMPLE PROCESSING DEVICES, SYSTEMS AND METHODS (Attorney Docket No. 56047USA29).

The documents identified above all disclose a variety of different constructions of sample processing devices that could be used to manufacture sample processing devices according to the principles of the present invention. For example, although many of the sample processing devices described herein

are attached using adhesives (e.g., pressure sensitive adhesives), devices of the present invention could be manufactured using heat sealing or other bonding techniques.

One illustrative sample processing device manufactured according to the principles of the present invention is illustrated in Figures 1 and 2. The sample processing device 10 includes at least one, and preferably a plurality of process arrays 20. Each of the process arrays 20 extends from proximate a first end 12 towards the second end 14 of the sample processing device 10.

The process arrays 20 are depicted as being substantially parallel in their arrangement on the sample processing device 10. Although this arrangement may be preferred, it will be understood that any arrangement of process arrays 20 that results in their substantial alignment between the first and second ends 12 and 14 of the device 10 is sufficient.

Alignment of the process arrays 20 between the first and second ends 12 and 14 is important because sample materials are distributed throughout the sample processing device by rotation about an axis of rotation proximate the first end 12 of the device 10. When so rotated, any sample material located proximate the first end 12 is driven toward the second end 14 by centrifugal forces developed during the rotation.

Each of the process arrays 20 includes at least one loading chamber 30, at least one main conduit 40, and a plurality of process chambers 50 located along each main conduit 40. It may be preferred that each of the process arrays include only one loading chamber 30 and only one main conduit 40. The process chambers 50 are in fluid communication with the main conduit 40 through feeder conduits 42. As a result, the loading chamber 30 in each of the process arrays 20 is in fluid communication with each on the process chambers 50 located along the main conduit 40 leading to the loading chamber 30. Each of the process arrays 20 depicted in Figure 1 also includes an optional drain chamber 22 located at the end of the main conduit 40.

Each of the loading chambers 30 includes an inlet port 32 for receiving sample material into the loading chamber 30. The sample material may be

delivered to port 32 by any suitable technique and/or equipment. A pipette 11 is depicted in Figure 1, but is only one technique for loading sample material into the loading chambers 30. The pipette 11 may be operated manually or may be part of an automated sample delivery system for loading the sample material into loading chambers 30 a sample processing device 10.

Each of the process arrays 20 in the sample processing devices 10 of the present invention are preferably unvented. As used in connection with the present invention, an "unvented" process array is a process array in which the only ports leading into the volume of the process array are located in a loading chamber of the process array. In other words, to reach the process chambers within an unvented process array, sample materials must be delivered to the loading chamber through a port located in the loading chamber. Similarly, any air or other fluid located within the process array before loading with sample material must also escape from the process array through a port or ports located in the loading chamber. In contrast, a vented process array would include at least one opening outside of the loading chamber. That opening would allow for the escape of any air or other fluid located within the process array before loading during distribution of the sample material within the process array.

As seen in Figure 2, the process chamber 50 defining a volume 52 that may include a reagent 54. It may be preferred that at least some, and preferably all, of the process chambers 50 in the devices 10 of the present invention contain at least one reagent before any sample material is distributed. The reagent 54 may be fixed within the process chamber 50 as depicted in Figure 2. The reagent 54 is optional, i.e., sample processing devices 10 of the present invention may or may not include any reagents 54 in the process chambers 50. In another variation, some of the process chambers 50 may include a reagent 54, while others do not. In yet another variation, different process chambers 50 may contain different reagents.

Other features depicted in the sample processing device 10 are a first major side 16 and a second major side 18, between which the volume 52 of process chamber 50 is formed. Also depicted in Figure 2 is a portion of feeder

conduit 42 used to deliver sample material to the process chamber 50. The major sides 16 and 18 of the device 10 may be manufactured of any suitable material or materials. Examples of suitable materials include polymeric materials (e.g., polypropylene, polyester, polycarbonate, polyethylene, etc.), metals (e.g., metal foils), etc.

It may be preferred that at least one of the first and second major sides 16 and 18 be constructed of a material or materials that substantially transmit electromagnetic energy of selected wavelengths. For example, it may be preferred that one of the first and second major sides 16 and 18 be constructed of a material that allows for visual or machine monitoring of fluorescence or color changes within the process chambers 50.

It may also be preferred that at least one of the first and second major sides 16 and 18 be in the form of a metallic foil. The metallic foil may include a passivation layer on the surfaces that face the interiors of the loading chambers 30, main conduits 40, feeder conduits 42, and/or process chambers 50 to prevent contamination of the sample materials.

In the illustrative embodiment of the sample processing device depicted in Figures 1 and 2, the first major side 16 is preferably manufactured of a polymeric film (e.g., polypropylene) that is formed to provide structures such as the loading chambers 30, main conduit 40, feeder conduits 42, and process chambers 50. The second major side 18 is preferably manufactured of a metallic foil, e.g., an aluminum or other metal foil. The metallic foil is preferably deformable as discussed in more detail below.

The first and second major sides 16 and 18 may be attached by any suitable technique or techniques, e.g., heat sealing, ultrasonic welding, etc. It may, however, be preferred that the first and second major sides 16 and 18 be attached using adhesive. As depicted in Figure 2, the adhesive may preferably be provided in the form of a layer of adhesive 19. It may be preferred that the adhesive layer 19 be provided as a continuous, unbroken layer over the surface of at least one of the first and second major sides 16 and 18. It may, for example,

be preferred that the adhesive layer 19 be provided on the metallic foil of major side 18.

A variety of adhesives may be used, although any adhesive selected should be capable of withstanding the forces generated during processing of any sample materials located in the process chambers 50. Those forces may be large where, e.g., the processing involves thermal cycling as in, e.g., polymerase chain reaction and similar processes. The adhesives may include, e.g., hot melt adhesives, curable adhesives, pressure sensitive adhesives, etc.

Among the pressure sensitive adhesives that may be used in connection with the sample processing devices of the present invention are those that are resistant to high temperatures and humidity. It may, for example, be preferred to use silicone pressure sensitive adhesives. Examples of some suitable silicone-based pressure sensitive adhesives are silicone-polyurea compositions as described in, e.g., U.S. Patents 5,461,134 and 6,007,914 or International Publication No. WO 96/35458 that contain a sufficient level of tackifying resin to provide the desired tackiness to the composition.

It may be preferred that all features, e.g., loading chambers 30, main conduit 40, feeder conduit 42, process chambers 50, and drain chambers 22, be formed in the first major side 16 while the second major side 18 is substantially flat. By locating all of the features in one side of the sample processing device 10, the need for aligning the two sides together before attaching them may be eliminated. Furthermore, a flat second major side 18 may promote intimate contact with, e.g., a thermal block such as that used in thermal cycling equipment. Alternatively, however, it will be understood that features may be formed in both sides 16 and 18 of sample processing devices according to the present invention.

Another potential feature of the sample processing devices of the invention is isolation of the process chambers 50 by closing the fluid pathways in the devices 10. Referring now to Figures 2 and 3, the process chambers 50 may be isolated after distribution of any sample materials by deforming the second major side 18 such that it extends into one or both of the main conduits 40 or the

feeder conduits 42 in each of the process arrays 20. Figure 3 illustrates one such closure method where the second major side 18 is deformed into the main conduit 40, with the adhesive layer 19 located between the two sides.

The desire to hermetically seal fluid pathways in the sample processing devices 10 of the present invention may lead towards the use of pressure sensitive adhesive for the adhesive layer 19. Where a pressure sensitive adhesive is present between the first and second major sides 16 and 18 of the device, deformation of the second major side 18 may result in adhesion between the first and second major sides 16 and 18 in the deformed area. That adhesion may enhance any sealing or closure produced by the deformation. The need for hermetic sealing may be more acute when the sample processing devices are to be used in thermal processing reactions such as, e.g., polymerase chain reaction, in which any liquids in the devices can exert high pressures on the seals due to thermal expansion.

After distribution of sample materials into the process chambers 50 is completed, it may be desirable to isolate the process chambers 50 from each other. Isolation may be accomplished in a variety of manners. For example, isolation of the process chambers 50 may involve deformation of the feeder conduits 42 and/or main conduits 40 within each of the process arrays 20.

For those sample processing devices that include a metallic layer, isolation of the process chambers 50 may involve plastic deformation of the metallic layer to close the main conduits 40 and/or feeder conduits 42. If, for example, a pressure sensitive adhesive 19 is used to attach the first and second major sides 16 and 18 of the sample processing device together, that same pressure sensitive adhesive may improve the sealing of main conduits 40 and/or feeder conduits 42 by adhering the deformed first and second major sides 16 and 18 together.

It should be understood, however, that complete sealing of the deformed portions of the sample processing device 10 may not be required. For example, it may only be required that the deformation restrict flow, migration or diffusion

through a conduit or other fluid pathway sufficiently to provide the desired isolation.

In one method in which the process arrays 20 are closed after distribution of sample materials into process chambers 50, it may be necessary to deform only a portion of the main conduit 40 or, alternatively, the entire length of the distribution channel 40. Where only a portion of the main conduit 40 is deformed, it may be preferred to deform that portion of the main conduit 40 located proximate the loading chamber 30.

Sealing all of the main conduit 40 by forcing the sides 16 and 18 together along the length of the conduit 40 may provide advantages such as driving any fluid located in the main conduit 40 back into the loading chamber 30. One potential advantage, however, of sealing only a portion of the main conduit 40 is that either none or only a small amount of any fluid material located in the main conduit 40 would be returned to the loading chamber 30.

Methods of distributing sample materials by rotating a sample processing device according to the present invention will now be described with reference to Figure 4. After providing a sample processing device 10' that includes first and second opposing ends 12' and 14' with at least one process array 20' aligned between the ends 12' and 14' of the device 10', sample material may be delivered to the process chambers 50'of the process array 20' by rotating. It should be noted that the sample processing device 10' includes only one process array 20' with a single loading chamber 30' connected to the process chambers 50' along two main conduits 40'.

The amount of sample material delivered to each of the loading chambers on the devices 10' may vary. It may, however, be preferred that the volume of sample material delivered to each of the loading chambers is no greater than the combined volumes of any main conduits, feeder conduits, and process chambers in fluid communication with the loading chamber. Where an optional drain chamber (see, e.g., Figure 1) is located at the distal and of the process array, the amount of sample material delivery to each of the loading chambers may be

increased to compensate for the additional volume of the process array downstream from the loading chamber.

After the loading chambers contain the desired sample material, that sample material must be transported to the process chambers within each of the process arrays. Referring to Figure 4, the distribution of sample material is effected by rotating the sample processing device 10' about an axis of rotation 15' located proximate the first end 12' of the sample processing device 10'. Rotation of the device 10' about the axis of rotation 15'when so oriented will result in centrifugal forces on any sample materials located within the loading chamber 30'. The centrifugal forces will drive the sample material out of the loading chamber 30' and into the main conduits 40' for delivery to the process chambers 50'.

The sample processing device 10' is oriented such that the process chambers 50' are located further from the axis of rotation 15'than the loading chamber 30'. The sample processing device 10' is located on a platter 17' that rotates about the axis 15'. The platter 17' may preferably be capable of accepting more than one sample processing device 10' for simultaneous rotation about axis 15'.

The orientation of the sample processing devices relative to the axis of rotation 15' is not critical, provided that the process chambers are located further from the axis of rotation 15' than the loading chambers. For example, where the sample processing device 10' is in the form of a substantially flat card-like article, the edge of the first end 12' of the sample processing device 10' may be oriented substantially perpendicular to the axis of rotation as depicted in Figure 4. Alternatively, the axis of rotation 15' may be substantially aligned with (e.g., parallel to) the edge of the first end 12' of the sample processing device 10. A multitude of orientations of the first end 12' relative to the axis 15' can be envisioned between parallel and perpendicular, all of which are acceptable as long as the process chambers are distal from the axis 15'relative to the loading chambers on the devices.

Because the process arrays of sample processing devices according to the present invention are preferably unvented as described above, distribution of sample materials to the process chambers may be difficult due to the air or other fluids trapped within the process chambers. Among the techniques that may be used to assist in distribution of the sample materials are selection of the materials used to construct the sample processing device, the addition of materials to the sample material (e.g., the addition of a surfactant to reduce surface tension in the sample material), manipulation of the viscosity of the sample material (e.g., by heating), etc.

One advantage of centrifugal loading of sample materials into process chambers is the ability to rotate the sample processing device and inspect the device after an initial period of rotation to determine whether sample material has been adequately distributed to the process chambers. If distribution is not satisfactory, the sample processing device can be rotated again until satisfactory sample material distribution is obtained.

In addition to, or in place of, a sequential rotate-inspect-rotate approach, the methods of the present invention may also employ two or more acceleration/deceleration cycles to assist in distribution of sample materials from the loading chambers to the process chambers. Alternating acceleration and deceleration of the device during rotation may essentially burp the sample materials through main conduit and feeder conduits (if any) into process chambers. It may also be helpful if the acceleration and/or deceleration are rapid. The rotation may also preferably only be in one direction or it may be in opposite directions.

The actual acceleration and deceleration rates may vary based on a variety of factors such as temperature, size of the sample processing device, size of the conduits and chambers, distance of the sample material from the axis of rotation, materials used to manufacture the devices, properties of the sample materials (e.g., viscosity), etc. one example of a useful acceleration/deceleration cycle may include an initial acceleration to about 4000 revolutions per minute (rpm), followed by deceleration to about 1000 rpm over period of about 1

second, with oscillations in rotational speed of the device between 1000 rpm and 4000 rpm at 1 second intervals until a sample materials are distributed.

In addition to constant speed rotation and acceleration/deceleration cycling during rotation, the methods of the present invention may also include vibration of the sample processing device to assist in the distribution of sample materials into process chambers. Vibration, such as tapping, high frequency oscillations, etc., may assist in removal of entrapped air bubbles located within the conduits or process chambers. Vibration of the sample processing device may be employed before or after rotation, or it may be employed during rotation of the sample processing device about the axis of rotation.

Although the process chambers illustrated in device 10 of Figure 1 appear substantially circular in shape, it should be understood that the process chambers used in sample processing devices of the present invention may take any suitable shape. One example of an alternative shape is depicted in Figure 5 in which the process chambers 150 are in the form of oval shapes that are elongated along axis 151. The axis 151 is preferably generally aligned with the main conduit 140. As a result, the axis 151 will generally extend from the first end of the sample processing device to its second end, with the oval shapes of process chambers 150 having their largest dimension aligned between the first and second ends of the sample processing device.

Figure 5 also depicts feeder conduits 142 that are preferably angled off of the main conduit 140 and adjoin the process chambers 150 at one end. It may be further preferred that the feeder conduits 142 meet the process chambers 150 at the end closest to the first end of the sample processing device (which is, therefore, the end of the process chamber that is closest to the axis of rotation during loading). Entry of the feeder conduits 142 into the process chambers 150 at the end may facilitate removal of air within the chambers 150 during loading.

The feeder conduit angle ß, i.e., the included angle formed between the feeder conduits 142 and the main conduit 140, may also enhance filling of the process chambers 150 by promoting the removal of the air. It may, for example, be preferred that the feeder conduit angle be less than 90 degrees, more

preferably less than 75 degrees. The feeder conduit angle will always be measured between the side of the feeder conduit 142 facing away from the first end of the device and the main conduit 140.

Another potentially advantageous optional feature illustrated in Figure 5 is the longitudinal offset of the feeder conduits 142 on opposing sides of the main conduit 140 (as opposed to the cross-conduit alignment of the feeder conduits 42 in Figure 1). That offset between the points at which the opposing feeder conduits 142 join the main conduit 140 may assist in preventing cross-chamber contamination during filling and/or processing.

Figures 6 and 7, in conjunction with Figure 5, illustrate yet another optional feature of the sample processing devices of the present invention. Figure 6 is a cross-sectional view of Figure 5 taken along line 6-6 in Figure 5 and Figure 7 is a cross-sectional view of Figure 6 taken along line 7-7 in Figure 6. The figures illustrate the smaller cross-sectional area of the feeder conduit 142 as compared to the main conduit 140. The different cross-sectional area of the conduits 140 and 142 is achieved, in the illustrated embodiment, by different heights and widths in the two conduits. Providing conduits with different cross-sectional areas may limit diffusion of sample material from the process chambers 150 into the main conduit 140 after and/or during filling. By limiting diffusion, cross-chamber contamination may also be reduced.

Figure 8 is a schematic diagram illustrating another arrangement for process arrays 220 useful in sample processing devices of the invention. Among the features depicted in connection with process arrays 220 are the staggered relationship between loading chambers 230. Such a staggered relationship may improve the density or spacing between process chambers 250.

Each of the loading chambers 230 also includes a loading port 232 and a vent port 234 which may facilitate rapid filling of the loading chambers 230 by providing a pathway separate from the loading port 232 for air to escape during filling of the loading chamber 230.

Another feature depicted in Figure 8 is the serial relationship between the process chambers 250 located along each of the main conduits 240. Each pair of

successive process chambers 250 is in fluid communication with each other along main conduit 240. As a result, if any reagents or other materials are to be located within process chambers 250 before distribution of the sample material, then some mechanism or technique for preventing removal of those materials during distribution of the sample material must be provided. For example, the reagents may be contained in a wax or other substance within each of the process chambers 250.

Figure 9 is a schematic diagram illustrating yet another arrangement of process arrays 320 that may be used in connection with sample processing devices of the present invention. Each of the process arrays 320 includes a loading chamber 330 that, in turn, includes a loading port 332 and a vent port 334. The loading chambers 330 are in fluid communication with a plurality of process chambers 350 through main conduits 340.

One feature illustrated in connection with Figure 9 is the addition of valves 344 along the main conduits 340. Each of the main conduits 340 bifurcates to an individual subset of process chambers 350. By selectively opening or closing the valves 344 (which may be either closed or open when manufactured) the delivery of sample material to each subset of process chambers 350 may be enabled or prevented. For example, if one of the valves 344 is open while the other valve 344 is closed, delivery of sample material will be effected only to one subset of process chambers 350 (through the open valve 344).

It may be possible to achieve the same result, i.e., enabling or preventing delivery of sample material to a subset of process chambers 350, by sealing the main conduit 340 at an appropriate location after the bifurcation point. The use of valves 344 may, however, provided the ability for automated control or customization of the sample processing device including process arrays 320. The valves 344 may take any suitable form, some examples of which are described in the patent applications identified above.

By using customizable process arrays 320, it may be possible to provide sample processing devices that are tailored at the point of use for particular

testing needs. Other advantages may be found in the ability to reduce the volume of sample material needed by reducing the number of process chambers 350 to which that sample material may be delivered. Alternatively, where a higher level of confidence is required, the valves 344 may be opened to increase the number of process chambers 350 to which sample material is delivered, thereby increasing the number of tests performed.

Referring now to Figure 10, another optional feature of the present invention is separation of the loading chambers 430 from the remainder of the sample processing device 410. Separation of the loading portion of the sample processing device 410 from the portion containing the process chambers 450 may provide advantages such as, for example, reducing the size of the sample processing device 410, reducing the thermal mass of the sample processing device 410, removing any sample materials that may remain within the loading chambers 430 after distribution to process chambers 450, etc.

Separation of the loading chambers 430 from the sample processing device 410 may involve, for example, cutting the sample processing device 410 along the separation line 413 as depicted in Figure 10. Where the loading chambers 430 are to be physically separated from the remainder of the sample processing device 410, it is typically preferable that the main conduits 440 be sealed across at least the separation line 413 to prevent leakage of the sample materials during and after the separation process.

The use of a pressure sensitive adhesive within the main conduits 440 (see, e.g., Figures 2 and 3) may be particularly helpful to ensure adequate sealing of the main conduits. In addition to, or in place of, pressure sensitive adhesives within the conduits 440, it may be desirable to further seal the main conduits 440 by, e.g., the application of heat and/or pressure to bond the conduit closed.

If additional sealing is required, it may also be helpful to cover the ends of the main conduits with a seal 444 as illustrated in Figure 11. The seal may be provided, e.g., in the form of an adhesive coated foil or other material. Alternatively or in addition to the use of an adhesive to secure the seal 444, it

may be desirable to, e.g., heat seal the seal 444 in place on the sample processing device 410.

Referring now to Figures 12 and 13, one alternative to physical separation of the loading chambers 530 from the remainder of the sample processing device 510 may include folding the sample processing device 510 along, e.g., separation line 513. That folding process may also close the main conduit 540 across the separation line 513 by crimping the main conduits 540, such that a desired level isolation may be achieved between the process chambers 550 without further deformation of any of the main conduits 540 or the feeder conduits 542.

It may be desirable to provide crimping areas 546 located at the intersections of the main conduits 540 with the folding line 513 that are wider and shallower than the surrounding portions of conduits 540 to facilitate crimping of the conduits 540 during folding. The wider, shallower crimping areas 546 do, however, preferably provide a cross-sectional area for fluid flow that is similar to the cross-sectional fluid flow area of the surrounding portions of the main conduits 540.

The centrifugal forces developed during rotation of the sample processing devices to deliver the sample materials to process chambers may challenge the sealing of the process chambers and other fluid pathways in each of the process arrays. The challenges may be especially acute when the sample processing device is constructed using an adhesive to attach to layers together.

To assist with the sealing of the process chambers and other fluid pathways on the sample processing devices during rotation, it may be advantageous to compress the major sides of the sample processing devices together during rotation. Referring to Figure 14, the sample processing device 610 may, for example, be located within a compression device 660 (e.g., in the form of a clamshell or other suitable structure) that compresses the major sides of the sample processing device 610 together during rotation. The compression device 660 may, for example, include conformable material 662 in contact with

one side of the sample processing device 610. The conformable material 662 may, for example be a resilient foam or similar composition.

Also included in the compression device 660 is a base 664 in contact with the opposing side of the sample processing device 610. As the conformable material 662 and the base 664 are biased toward each other, the major sides of the sample processing device 610 are compressed. That compression may significantly reduce or prevent leakage of any sample materials out of the process chambers or other fluid pathways during rotation of the sample processing device 610.

The conformable material 662 is preferably located in contact with the side of the device 610 that includes any structures such as process chambers or conduits protruding therefrom to avoid damaging those structures. The base 664 may be formed of any suitable material which may be rigid where no structures are protruding from the side of the device 610 facing the base 664.

A portion of an alternative compression device is depicted in Figures 15 and 16 in connection with a process chamber 650' and portion of a feeder conduit 642'. The alternative compression device is designed to provide pressure. The compression device includes a shaped compression die 662' that applies pressure about the periphery of the process chamber 650' and the feeder conduit 642'. The compression die 662' preferably acts against a base 664' located on the opposite side of the sample processing device. Departing from the design of the compression device depicted in Figure 14, the compression die 662' may preferably be formed of a substantially rigid material

Figure 17 is an exploded perspective view of an assembly including a sample processing device 710 of the present invention and a carrier 780. Because, in many instances, the sample processing devices 710 are manufactured from materials that are relatively thin, it may be desirable to attach the device 710 to a carrier 780 for a variety of reasons. Among those reasons are the need to provide an assembly having sufficient thickness to be processed in existing thermal processing equipment with a minimum of modification to that equipment.

By providing a carrier 780 that is separate from the sample processing device 710, the thermal mass of the sample processing device 710 can be minimally affected as compared to manufacturing the entire sample processing device 710 with a thickness suitable for processing in conventional equipment. Another potential advantage of a carrier 780 is that the sample processing devices 710 may exhibit a tendency to curl or otherwise deviate from a planar configuration. Attaching the device 710 to a rigid carrier 780 can retain the sample processing device in a planar configuration for processing.

The carrier 780 may be attached to the sample processing device 710 in a manner that allows for the carrier 780 to be reused with many different sample processing devices 710. Alternatively, each carrier 780 may be permanently attached to a single sample processing device 710 such that, after use, both the sample processing device 710 and the carrier 780 are discarded together.

The sample processing device 710 may be manufactured as described above. The carrier 780 may include various features such as carrier openings 782 that are preferably aligned with the plurality of process chambers 750 in the device 710. By providing carrier openings 782, the process chambers 750 can be viewed from the side of the sample processing device 710 facing the carrier 780. One alternative to providing the plurality of carrier openings 782 is to manufacture the carrier 780 of a material (or materials) transmissive to electromagnetic radiation in the desired wavelengths. As a result, it may be possible to use a carrier 780 that is contiguous over the surface of the sample processing device 710, i.e., the carrier provides no openings for access to the process chambers 750.

The carrier 780 illustrated in Figures 17 and 18 may also provide advantages in the sealing or isolation of the process chambers 750 after loading. Figure 18 illustrates the rails 783 in the carrier 780 that extend along the length of the main conduits 740 in the associated sample processing device 710. The rails 783 may, for example, provide a surface against which the main conduits 740 of the sample processing device 710 may be pressed while the conduit is

deformed to isolate the process chambers 750 and/or seal the conduits 740 prior to separating the loading chambers 730 from the device 710.

In addition to their use during deformation of the main conduits 740, the rails 783 may also be relied on during, e.g., thermal processing to apply pressure to the conduits 740 (thereby potentially improving the seals formed along the main conduits 740). Furthermore, the use of rails 783 also provides an additional advantage in that they provide for significantly reduced contact between the sample processing device 710 and the carrier 780 while still providing the necessary support for sealing of the main conduits 740 on device 710. The importance of reducing contact between the carrier 780 and device 710 may be particularly important when the assembly is to be used in thermal processing of sample materials (e.g., polymerase chain reaction, etc.). As such, the carrier 780 may be characterized as being spaced from the sample processing device 710 between the main conduits 740 when the rails 783 are aligned with the main conduits 740.

Various alignment features are also illustrated in Figures 17 and 18, including structures that align the sample processing device 710 relative to the carrier 780, as well as structures that align the assembly of sample processing device 710 and carrier 780 relative to, e.g., a thermal processing system used to thermally cycle materials in the sample process chambers 750. Alignment may also be used in connection with a detection system for detecting the presence or absence of a selected analyte in the process chambers 750.

It may be preferred that the sample processing device 710 be aligned relative to the carrier 780 proximate a center of both of those articles (center 781 of carrier 780 being indicated in Figure 17). To prevent rotation of the sample processing device 710 relative to the carrier 780, at least two points of registration or contact are required. Because the device 710 and carrier 780 may be subjected to temperature extremes during processing, it may be desirable, for example, that the sample processing device 710 be fixedly connected to carrier 780 in the center of the two articles, while any additional points of attachment

provide for differential expansion/contraction between the device 710 and carrier 780.

The alignment structures used to align the assembly as a whole to, e.g., thermal cycling and/or detection equipment, include protrusions 774 that are preferably designed to extend through alignment openings 776 in the sample processing device 710. As a result, alignment of the assembly is based on structures found in carrier 780. One advantage to relying on the carrier 780 for alignment structures is that its construction will typically being more dimensionally stable and accurate as compared to the sample processing device 710.

Figure 19 illustrates yet another optional feature of carriers used in connection with the present invention. The carrier 880 is depicted with an optical element 888, e.g., a lens, that may assist in focusing electromagnetic energy directed into the process chamber 850 or emanating from the process chamber 850. The optical element 888 is depicted as integral with the carrier 880, although it should be understood that the optical element 888 may be provided as a separate article that is attached to the carrier 880.

Patents, patent applications, and publications disclosed herein are hereby incorporated by reference as if individually incorporated. It is to be understood that the above description is intended to be illustrative, and not restrictive. Various modifications and alterations of this invention will become apparent to those skilled in the art from the foregoing description without departing from the scope of this invention, and it should be understood that this invention is not to be unduly limited to the illustrative embodiments set forth herein.

**What is claimed is:**

1. A method of distributing sample material in a sample processing device, the method comprising:

providing a sample processing device that comprises first and second opposing ends and at least one unvented process array comprising a loading chamber located proximate the first end, a main conduit extending towards the second end, and a plurality of process chambers distributed along the main conduit, wherein the main conduit is in fluid communication with the loading chamber and the plurality of process chambers;

loading sample material in the loading chamber of each of the process arrays; and

transporting the sample material to at least some of the process chambers by rotating the sample processing device about an axis of rotation located proximate the first end of the sample processing device, wherein the process chambers are located further from the axis of rotation than the loading chambers.

2. A method according to claim 1, further comprising closing the main conduits between the loading chambers and the plurality of process chambers after transporting the sample material.

3. A method according to claim 2, wherein the sample processing device comprises first and second major sides attached with a layer of pressure sensitive adhesive, and wherein the closing comprises adhering the first and second major sides along the main conduit.

4. A method according to claim 1, further comprising closing the main conduits between the loading chambers and the plurality of process chambers after transporting the sample material, wherein the closing comprises folding the sample processing device along a line located between the loading chambers and the plurality of process chambers.

5. A method according to claim 1, further comprising separating the loading chambers from the sample processing device after transporting the sample material to the process chambers.

6. A method according to claim 5, further comprising closing the main conduits between the loading chambers and the plurality of process chambers after transporting the sample material and before separating the loading chambers.

7. A method according to claim 6, wherein the sample processing device comprises first and second major sides attached with a layer of pressure sensitive adhesive, and wherein the closing comprises adhering the first and second major sides along the main conduit.

8. A method according to claim 5, wherein the separating comprises cutting the sample processing device.

9. A method according to claim 1, wherein the rotating during transporting the sample material comprises at least two acceleration/deceleration cycles.

10. A method according to claim 1, further comprising inspecting the sample processing device after rotating to determine whether adequate distribution of the sample material into the process chambers has occurred.

11. A method according to claim 10, further comprising rotating the sample processing device after inspecting the sample processing device.

12 A method according to claim 1, wherein the sample processing device further comprises first and second major sides, and wherein the method further

comprises compressing at least a portion of the first and second major sides of the sample processing device together.

13 A method according to claim 12 wherein the compressing comprises compressing the sample processing device within a discrete area located about a periphery of each of the process chambers.

14. A method according to claim 12, wherein the compressing is performed while rotating the sample processing device about the axis of rotation located proximate the first end of the sample processing device.

15. A method according to claim 1, further comprising vibrating the sample processing device.

16. A method according to claim 1, further comprising vibrating the sample processing device while rotating the sample processing device about the axis of rotation located proximate the first end of the sample processing device.

17. The method of claim 1, wherein the process chambers are elongated along an axis extending between the first and second opposing ends of the sample processing device.

18. The method of claim 1, wherein each of the process chambers is in fluid communication with the main conduit through a feeder conduit, and further wherein the feeder conduits form feeder conduit angles with the main conduit that are less than 90 degrees.

19. A sample processing assembly comprising:

a sample processing device comprising first and second opposing ends and at least one unvented process array comprising a loading chamber located proximate the first end, a main conduit extending towards the second end, and a

plurality of process chambers distributed along the main conduit, wherein the main conduit is in fluid communication with the loading chamber and the plurality of process chambers; and

a carrier attached to a first major side of the sample processing device, the carrier comprising a carrier body spaced from at least a portion of the first major side of the sample processing device.

20. The assembly of claim 19, wherein the carrier comprises a plurality of carrier openings, the plurality of carrier openings aligned with the plurality of process chambers in the sample processing device.

21. The assembly of claim 19, wherein the carrier comprises a rail aligned with the each of the main conduits on the sample processing device, wherein the carrier body is spaced from the sample processing device between adjacent main conduits.

22. The assembly of claim 19, wherein the sample processing device comprises first and second major sides attached with a layer of pressure sensitive adhesive, and wherein at least one of the main conduits is closed between the process chambers and the loading chamber by the pressure sensitive adhesive adhering to the first and second major sides together along the main conduit.

23. The assembly of claim 19, wherein the process chambers are elongated along an axis extending between the first and second opposing ends of the sample processing device.

24. The assembly of claim 19, wherein each of the process chambers is in fluid communication with the main conduit through a feeder conduit, and further wherein the feeder conduits form feeder conduit angles with the main conduit that are less than 90 degrees.

25. A sample processing device comprising:

first and second opposing ends;

a plurality of unvented process arrays, each of the process arrays comprising a loading chamber located proximate the first end; a main conduit extending towards the second end; and a plurality of process chambers distributed along the main conduit, wherein the main conduit is in fluid communication with the loading chamber and the plurality of process chambers; and

wherein each of the process chambers is in fluid communication with one of the main conduits through a feeder conduit, and wherein the feeder conduits form feeder conduit angles with the main conduits that are less than 90°.

26. The device of claim 25, wherein the process chambers are elongated along an axis extending between the first and second opposing ends of the sample processing device.

27. The device of claim 25, wherein the feeder conduits enter the process chambers proximate the first end of the device.

28. The device of claim 25, wherein the sample processing device comprises first and second major sides attached with a layer of pressure sensitive adhesive, and wherein at least one of the main conduits is closed between the process chambers and the loading chamber by the pressure sensitive adhesive adhering to the first and second major sides together along the main conduit.

29. The device of claim 25, further comprising a separation line located between the loading chambers and the plurality of process chambers, the separation line extending across the main conduits of each of the process arrays.

30. A device according to claim 29, wherein the separation line comprises a fold line.

Docket No. 55265USA9A.002

# CENTRIFUGAL FILLING OF SAMPLE PROCESSING DEVICES


## Abstract of the Disclosure

The present invention provides methods and devices for distributing sample material to a plurality of process chambers in a sample processing device by rotating the device about an axis of rotation. The process chambers are located along conduits extending from a loading chamber and, together, the loading chamber, conduits, and process chambers form process arrays that are aligned along a length of the sample processing devices. The process arrays are unvented, i.e., access to the interior volume of the process arrays is available only through the loading chamber. Also disclosed are methods of centrifugally loading sample material into the process chambers, as well as an assembly including a sample processing device and a carrier.

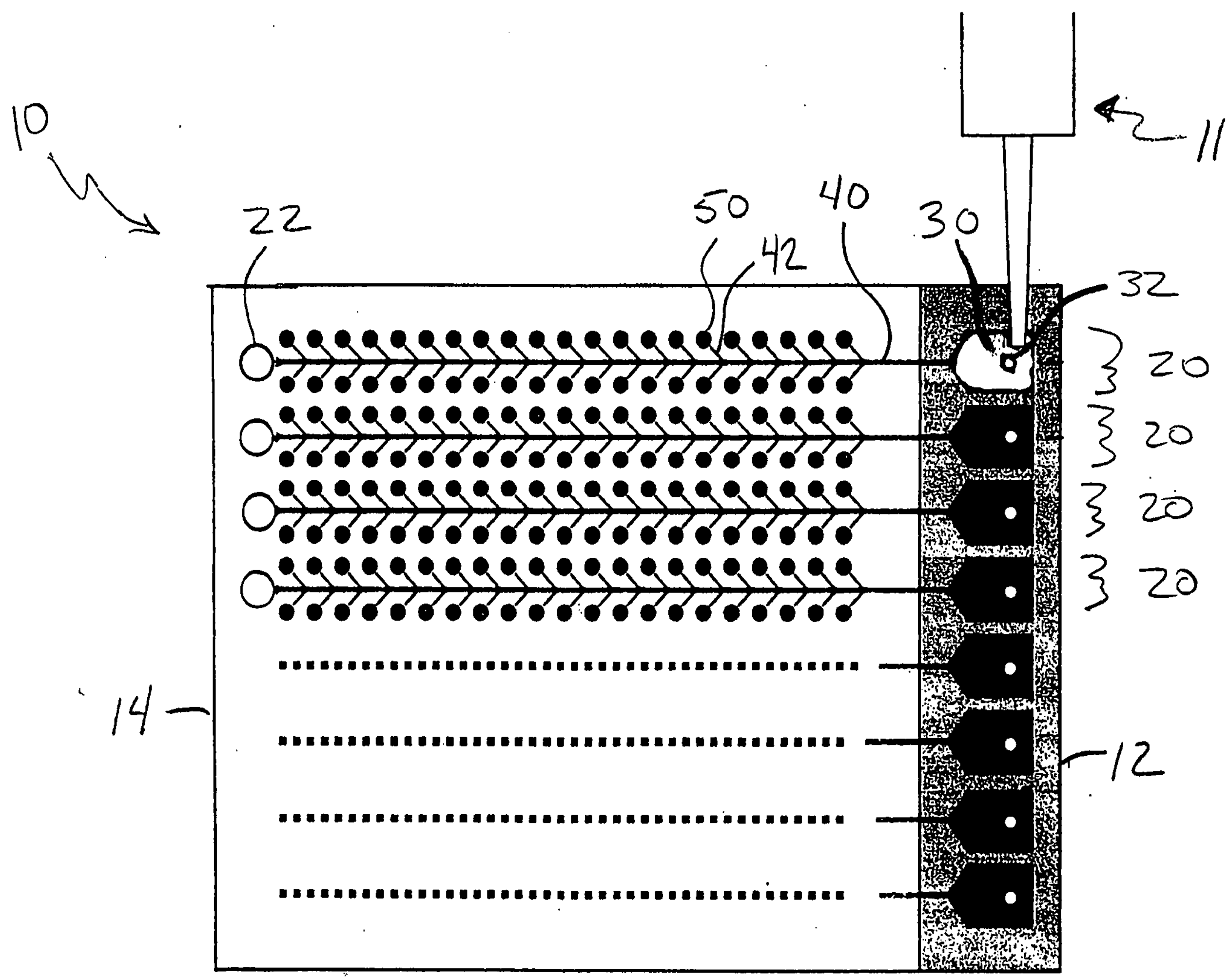


FIG. 1

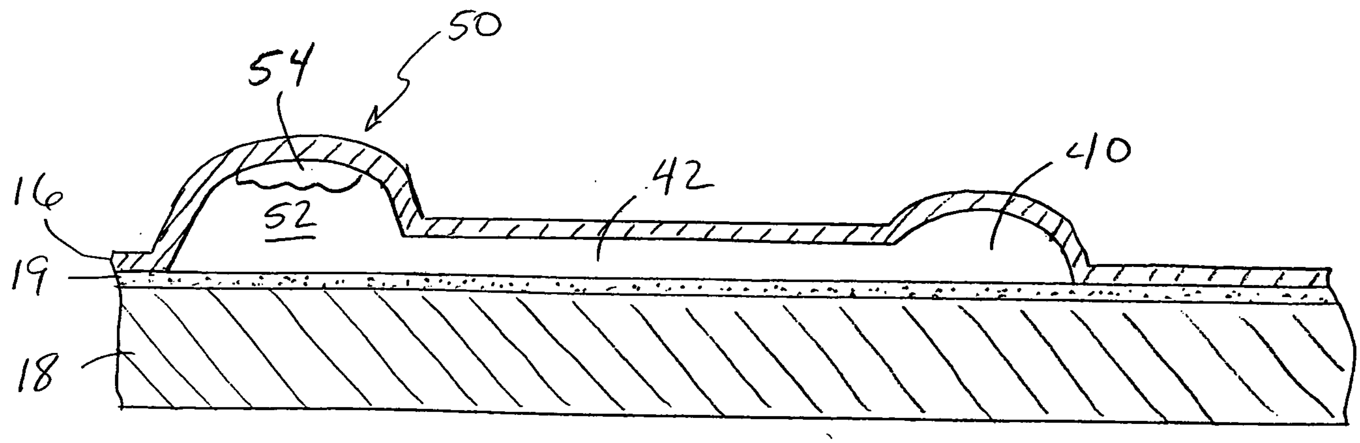


FIG. 2

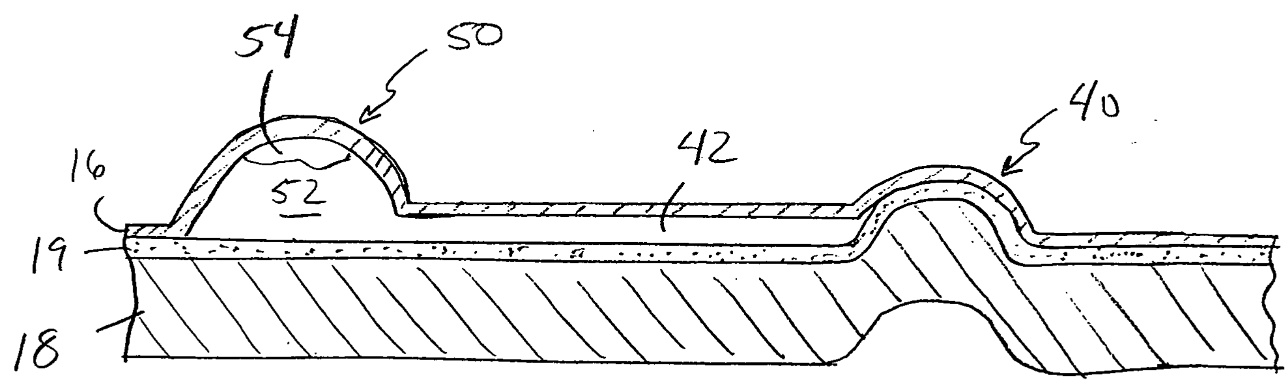


FIG. 3

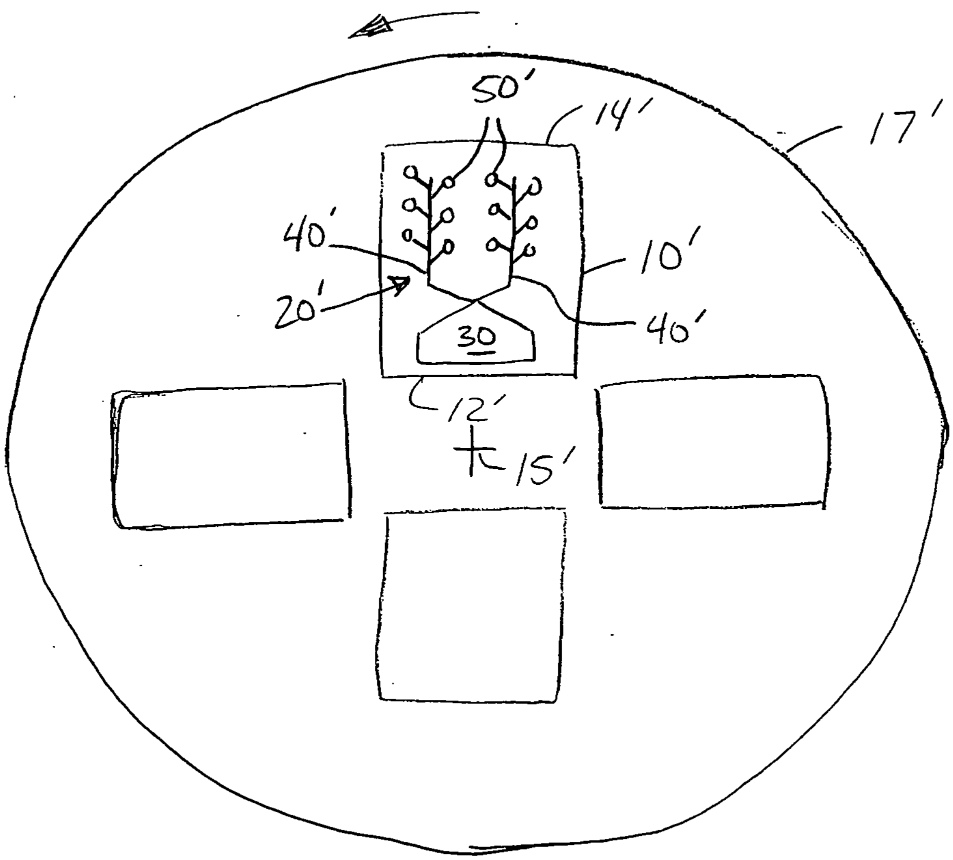


FIG. 4

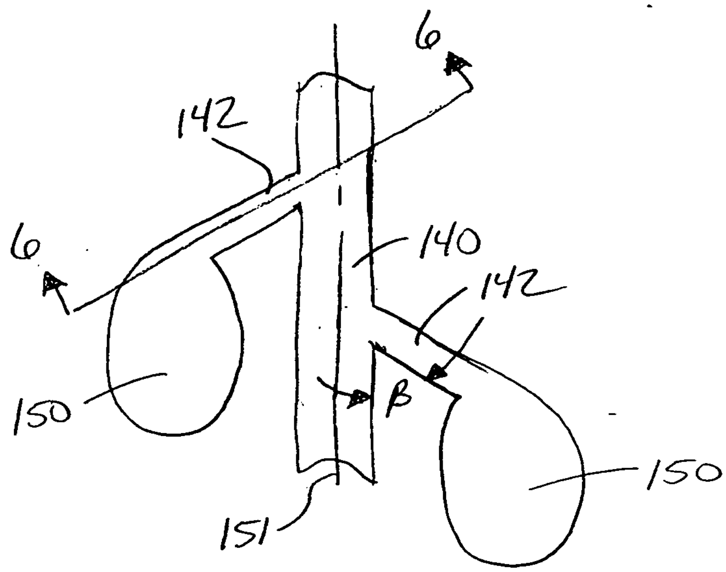


FIG. 5

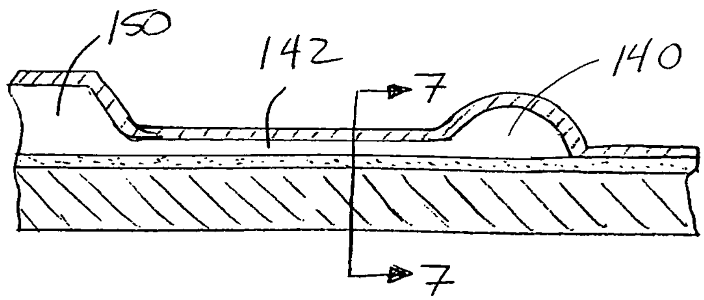


FIG. 6

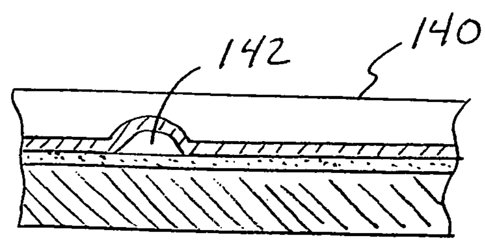


FIG. 7

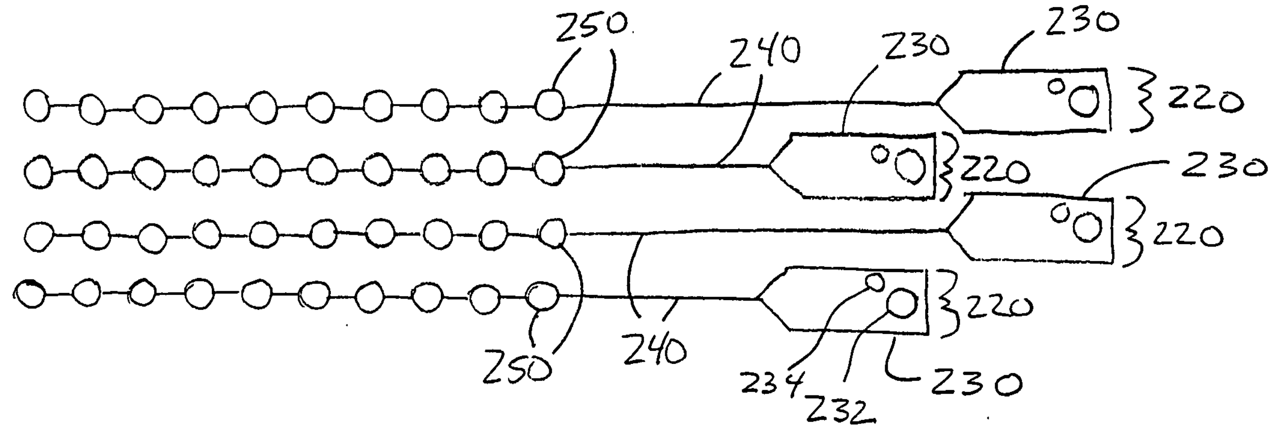

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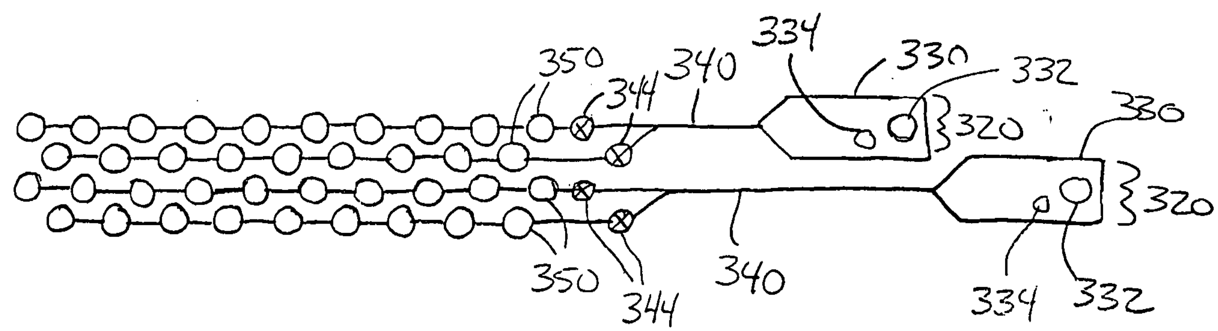
FIG. 8



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332

FIG 9

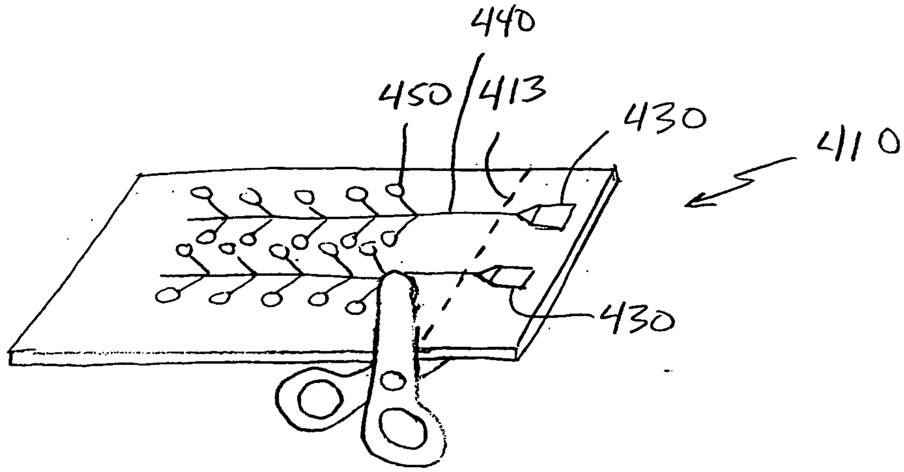


FIG. 10

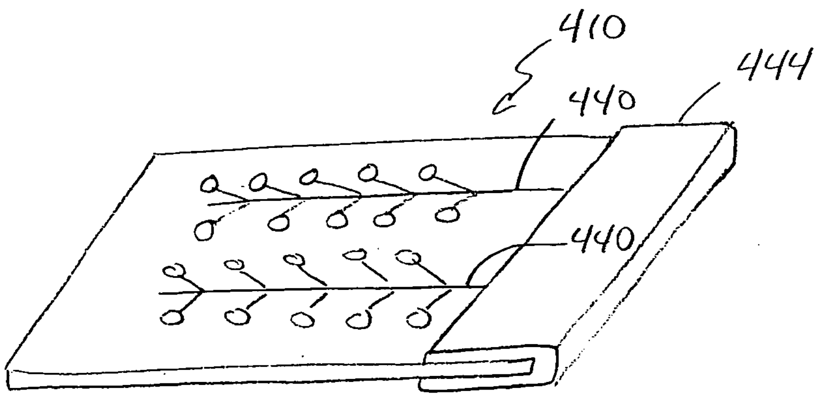


FIG. 11

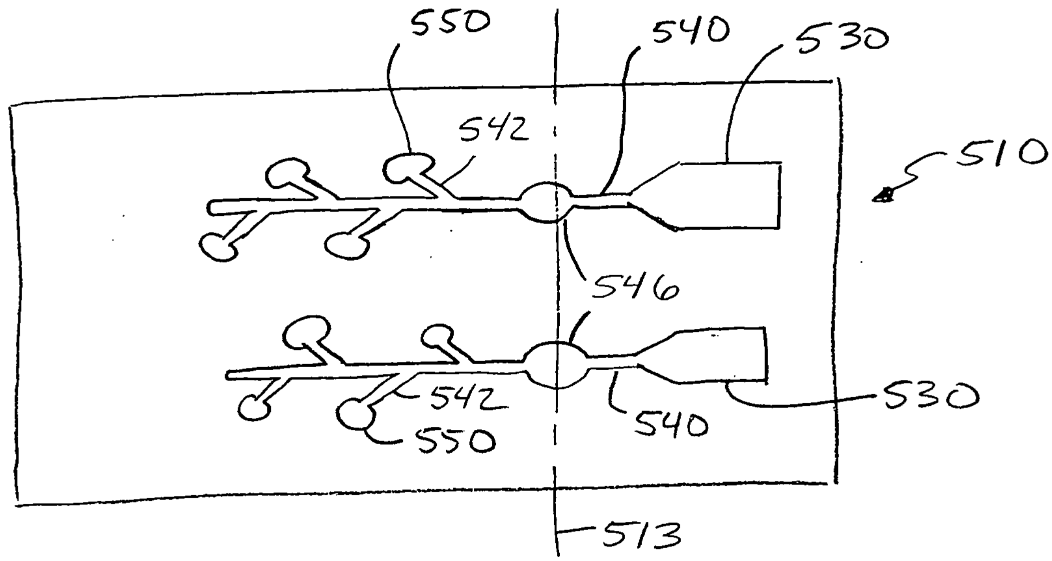


FIG. 12

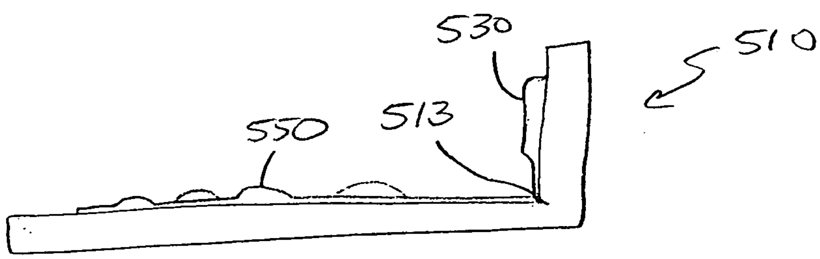


FIG 13

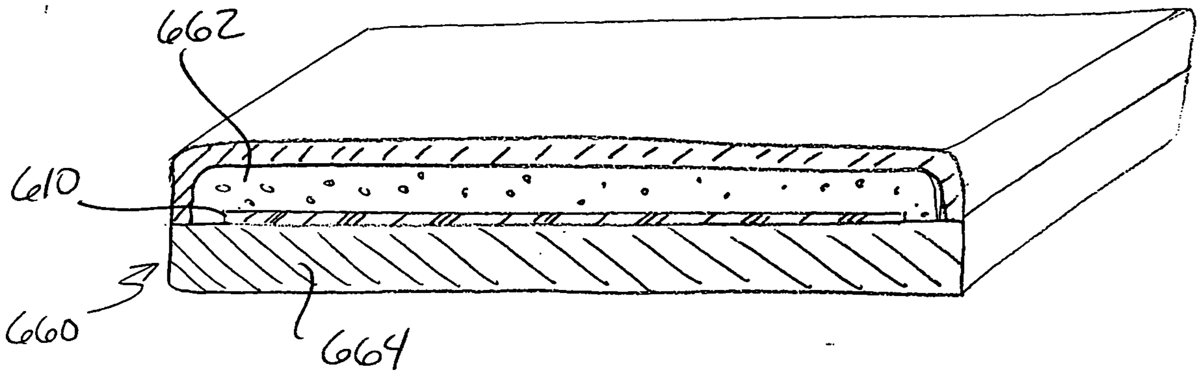


FIG. 14

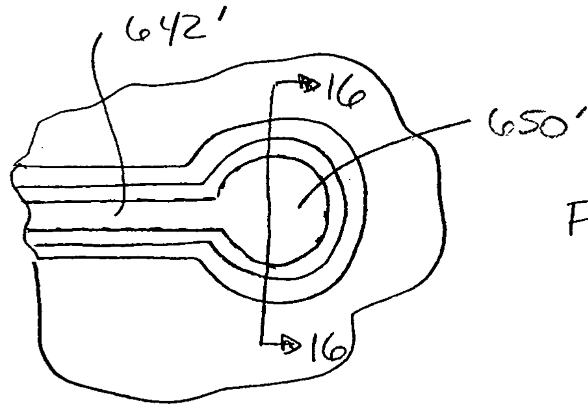


FIG. 15

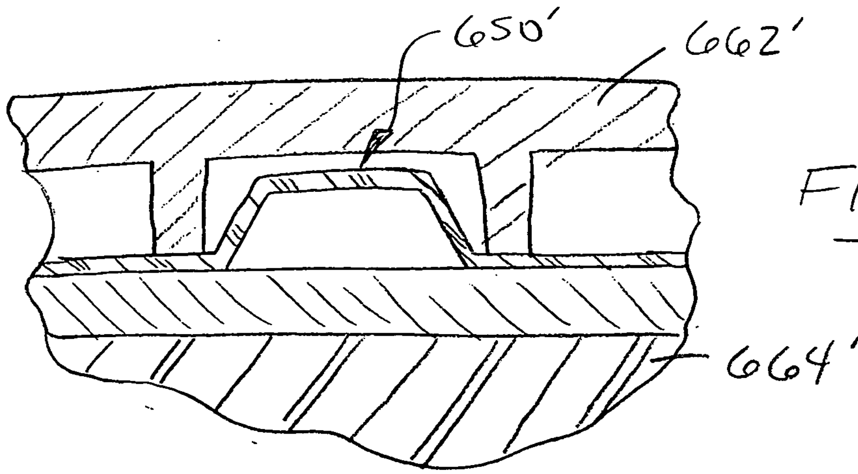


FIG. 16

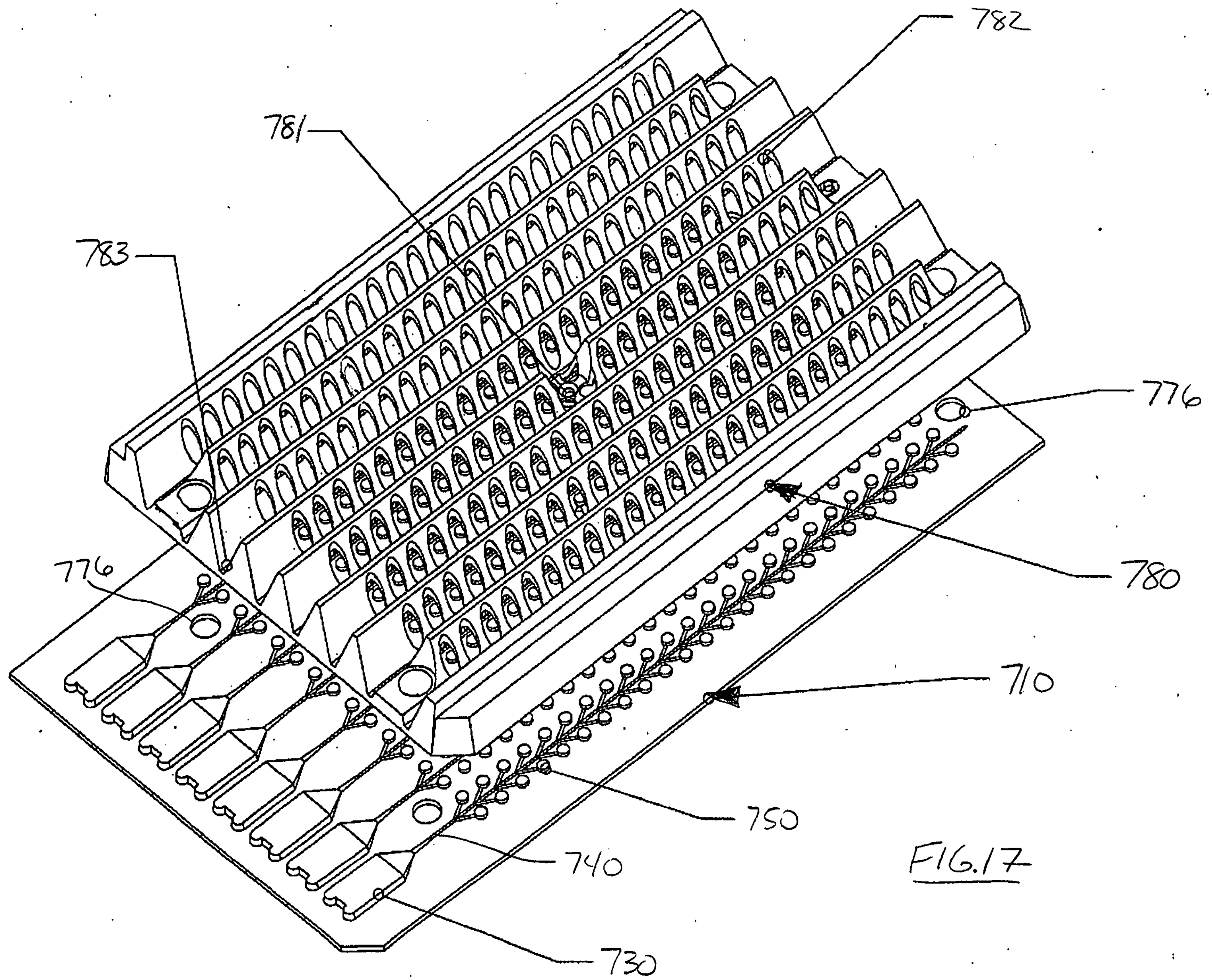


FIG.17

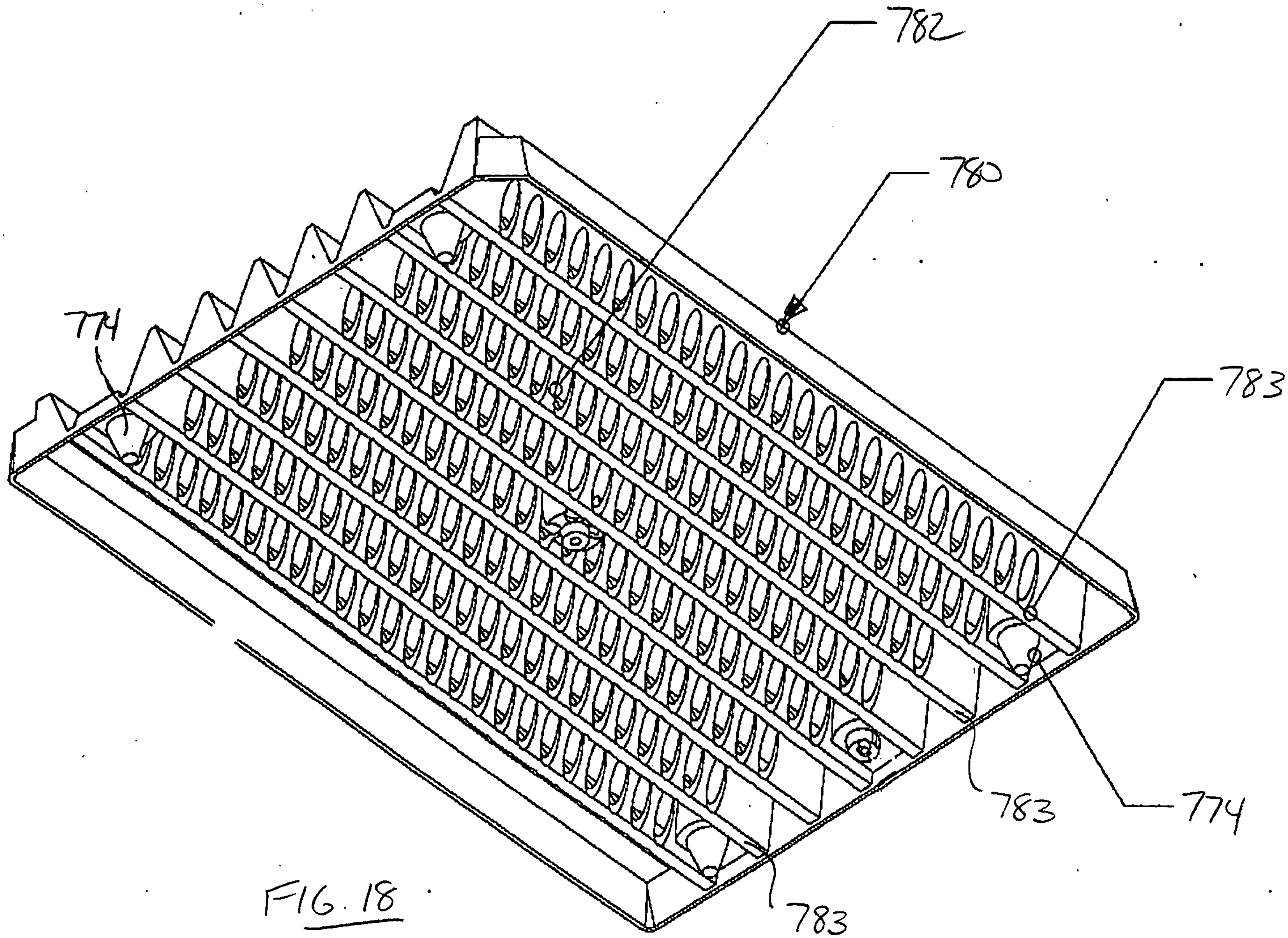


FIG. 18

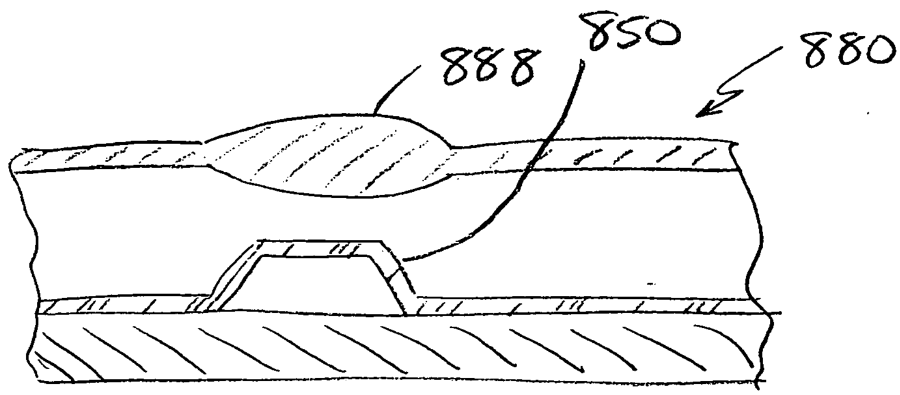


FIG. 19